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REVIEW

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Nature's blueprint for sugar metabolism: translating bee and ant strategies into human diabetes therapies

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Abstract

Despite advances in pharmacological treatments, diabetes mellitus remains a significant global health challenge, characterized by chronic hyperglycemia and associated metabolic dysfunctions. Effective and sustainable glycemic control remains elusive, prompting exploration into unconventional sources of metabolic insights. Social insects, in particular bees and ants, exhibit remarkable physiological adaptations enabling them to thrive on carbohydrate-rich diets without developing metabolic disorders typical in humans. This review investigates the bees and ants metabolic strategies to avoid metabolic disorders like diabetes, focusing on their enzymatic pathways such as trehalose metabolism, specialized hormonal regulation involving insulin-like peptides, adipokinetic hormones, and genetic and epigenetic mechanisms underpinning their metabolic resilience. By systematically comparing these insect adaptations with human metabolic systems, the proposed study identifies potential translational applications, including engineered probiotics, gene-editing approaches, and bioactive compounds for diabetes management. Furthermore, it explores technical, ethical, and ecological considerations for translating insect-derived metabolic mechanisms into human therapies. Highlighting both opportunities and challenges, this review emphasizes the need for interdisciplinary research to responsibly integrate nature-inspired solutions into modern diabetes care.

Keywords Diabetes mellitus, Bees, Ants, Metabolic resilience, Insulin-like peptides, Trehalose metabolism, Molecular metabolism, Metabolic syndrome

Introduction

Diabetes mellitus (DM) is acknowledged as one of the most relevant global health challenges, with prevalence rates rising sharply in diverse world areas, including both highly industrialized and resource-limited settings [1–3]. Characterized by chronic hyperglycemia resulting from deficits in insulin secretion, insulin action, or both, DM places an unprecedented strain on healthcare systems while remaining an unresolved multifactorial medical condition [4]. Despite notable advancements in pharmacological treatments and lifestyle interventions, achieving optimal glycemic control continues to be a significant hurdle in addressing its underlying metabolic dysfunctions. The search for innovative approaches in diabetes management has increasingly turned to unconventional

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sources, including ecological and biological adaptations in non-human organisms. Social insects, such as bees and ants, have emerged as compelling models for examining alternative metabolic strategies due to their exceptional tolerance for high-sugar diets and their ability to maintain metabolic homeostasis under carbohydrate-rich nutritional conditions [5, 6]. This review explores these metabolic adaptations and investigates their potential translational applications for improving diabetes prevention and treatment in humans.

Bees and ants, as eusocial insects, exhibit remarkable physiological mechanisms that allow them to efficiently utilize high-sugar resources without suffering from metabolic disorders typically associated with sugars rich diets in humans [7]. These adaptations include enzymatic pathways centered around trehalose metabolism, advanced sugar-storage processes, and robust hormonal regulatory systems such as those mediated by insulin-like peptides (ILPs) and adipokinetic hormone (AKH). Furthermore, genetic and epigenetic mechanisms in these insects provide additional layers of resilience, enabling precise energy regulation and metabolic flexibility [8]. By comprehensively analyzing these metabolic strategies, this paper aims to identify insights that could lead to the development of novel therapies and bioengineered solutions for diabetes management. Enzymatic systems enabling efficient sugar processing, the hormonal parallels between insect and human energy regulation, and the genetic adaptations that foster metabolic efficiency are among the areas of particular interest [9]. These insights are evaluated for their translational relevance in enhancing human glycemic control and mitigating insulin resistance.

The research aspect driving this review focuses on understanding how the metabolic adaptations of bees and ants can be leveraged to address key challenges in the prevention and treatment of diabetes mellitus. Addressing this health condition requires systematic comparative analyses of sugar metabolism in the mentioned insects and humans, with a focus on identifying evolutionary pathways and mechanisms that hold potential therapeutic applicability. The review further investigates bioengineering opportunities, e.g. the development of engineered probiotics, and gene-editing approaches inspired by insect metabolic efficiency, while also probing the technical, ethical, and ecological considerations involved in adapting these biological strategies to human medicine pharmacological approach. Acknowledging the complexity of translating insect-derived mechanisms into human therapeutic systems, this paper also highlights critical barriers to implementation, including biological compatibility and regulatory challenges, alongside potential solutions informed by interdisciplinary research.

The structure of this paper provides a logical and progressive exploration of the topic. An overview of the global burden of diabetes mellitus and examen of the limitations of current therapeutic approaches is presented. The dietary patterns and sugar-processing mechanisms of bees and ants, establishing the physiological basis for their metabolic resilience to carbohydrate-rich environments is described and analyzed, and, following this aspect, a detailed comparison of sugar metabolism in social insects and humans, with a focus on enzymatic, hormonal, genetic differences and similarities is proposed. Building on these foundations, the translational potential of insect-derived metabolic insights is explored, identifying opportunities for therapeutic innovation in diabetes management. In the following the challenges in applying these mechanisms to human biology are evaluated, the broader implications for sustainability and ethics are addresses. Forward-looking recommendations for research and ethical considerations outline necessary for responsibly integrating insect-based therapeutic strategies into modern medicine are discussed and evaluated.

Global epidemiology and burden of diabetes mellitus

Diabetes mellitus (DM) poses a major global health challenge, affecting over 450 million people and projected to rise to 700 million by 2045 [3]. This rise is driven by urbanization, sedentary lifestyles, unhealthy diets, and aging populations. These factors collectively complicate prevention efforts and require scalable interventions, such as early diagnosis and public health education [3].

The economic burden of DM is equally concerning, encompassing direct costs (treatment, medication) and indirect ones (productivity loss, premature death) [10]. Despite progress in pharmacological and lifestyle interventions, current therapies fall short of addressing the root causes of DM and often carry side effects that impair adherence [11]. Innovative approaches, including nanotechnology and gene-editing, offer promise but face challenges in cost, ethics, and implementation.

In populous countries like China, India, and the U.S., diabetes prevalence reflects unique socio-economic and cultural challenges [12]. In Sub-Saharan Africa, particularly Tanzania, healthcare disparities are exacerbated by limited access, financial barriers, and reliance on traditional medicine—highlighting the need for integrative, culturally sensitive care models [13].

Beyond physical health, diabetes—especially in children with type 1 DM—significantly impacts mental and social well-being [14]. Effective pediatric care should integrate mental health support, family involvement, and innovative tools to reduce treatment burden and improve quality of life.

Natural products, such as *Inocutis levis*-derived compounds, have shown multitarget antihyperglycemic effects, including enhancing glucose uptake and reducing oxidative stress [15]. These findings support the potential of bioactive metabolites as safer, holistic alternatives to synthetic drugs, though further research on bioavailability and delivery remains needed. In summary, diabetes management demands a multidimensional response that includes tailored public health strategies, integrative care in underserved regions, and exploration of nature-based therapeutics.

Current challenges and limitations in diabetes management

Current diabetes management strategies—pharmacological and lifestyle-based—often fall short in addressing the disease's multifactorial nature [16]. While drugs like sulfonylureas and SGLT2 inhibitors target glycemic control, they neglect underlying drivers such as oxidative stress and inflammation [17]. Side effects including hypoglycemia, gastrointestinal issues, and cardiovascular risks further hinder long-term adherence, highlighting the need for safer, broader-acting interventions. Combining conventional treatments with therapies targeting oxidative pathways remains underexplored.

Lifestyle changes, though essential, often face barriers like stress, financial constraints, and limited access to healthy foods or exercise spaces, especially in low-income populations [18]. Hence, integrated approaches that address psychological and social determinants of health are crucial. Personalized medicine and digital health platforms offer promising solutions to enhance compliance and tailor interventions. However, their widespread use is limited by infrastructure, cost, and the need for validation.

Globally, diabetes prevalence continues to rise, driven by urbanization, processed food intake, and sedentary habits [19, 20]. Urban–rural disparities highlight the need for context-specific interventions. Alarmingly, over 50% of diabetes cases remain undiagnosed, delaying treatment and increasing complication risks [21]. Mobile screening units and digital diagnostic tools could bridge these gaps, particularly in resource-limited settings.

In adolescents with type 1 diabetes, the burden includes high rates of depression and anxiety. Addressing this requires holistic care that combines mental health support with simplified self-management tools [22]. Family-based programs and gamified health apps have shown promise but need further evaluation. In many rural regions, such as Sub-Saharan Africa, reliance on traditional medicine due to limited healthcare access calls for integrative models combining modern and indigenous practices [13]. Mobile clinics and community health workers can enhance diagnosis and care delivery.

Innovative therapies like nanotechnology, gene therapy, and stem cell-based approaches hold potential but are constrained by cost, safety, and ethical concerns. Advances like CRISPR offer precision but raise regulatory challenges [23]. International collaboration is vital to scale and equitably distribute such technologies.

In summary, managing diabetes effectively requires a shift toward inclusive, integrated, and multidisciplinary models. While emerging technologies and natural-based interventions hold promise, systemic efforts are needed to ensure accessibility, safety, and long-term sustainability.

Rationale behind exploring novel therapeutic approaches from nature

The exploration of novel therapeutic approaches from natural sources has garnered significant attention in recent years, particularly in the management of diabetes mellitus. Flavonoids, naturally occurring secondary metabolites abundant in fruits, vegetables, and fungi, offer promising anti-diabetic properties due to their ability to regulate glucose metabolism through multiple mechanisms [24, 25]. These compounds target key cellular pathways, including hepatic enzymes, AMP-activated protein kinase (AMPK), peroxisome proliferator-activated receptors (PPARs), and nuclear factor kappa B (NF-kB), which are crucial in enhancing insulin sensitivity and optimizing glucose utilization. The role of flavonoids in modulating these pathways provides a multifaceted approach to addressing glucose dysregulation. By improving insulin signaling at the molecular level, flavonoids demonstrate their ability to directly alleviate one of the fundamental pathological features of diabetes. Their regulation of glucose transport, particularly through the enhancement of GLUT4 activity, allows for more effective cellular glucose uptake, contributing to improved glycemic control. This regulatory mechanism is particularly beneficial in combating insulin resistance, a common hallmark of type 2 diabetes [26]. Furthermore, flavonoids' multitarget activity sets them apart from synthetic drugs that often act on isolated pathways, offering a comprehensive strategy for both managing glycemic levels and mitigating diabetes-related complications, such as chronic inflammation and oxidative damage. This multitarget activity underscores the potential of flavonoids as both therapeutic agents and preventative tools, as their inclusion in diets has been shown to reduce the risk of developing insulin resistance. Beyond their clinical potential, the wide availability and sustainability of flavonoids, especially in low-resource settings, address the critical need for cost-effective and accessible diabetes

management solutions, further amplifying their relevance [27–30].

The remarkable metabolic adaptations of social insects, such as bees and ants, to high-sugar diets present a unique framework for understanding potential biological strategies for diabetes prevention and treatment. These insects thrive on carbohydrate-rich diets, including nectar and honeydew, which are high in simple sugars like glucose and sucrose. Despite constant exposure to high sugar intake, they maintain metabolic homeostasis and avoid conditions such as insulin resistance or metabolic overload, which are common in humans. This metabolic resilience is facilitated by specialized enzymatic pathways, such as those involving trehalose-6-phosphate synthase and trehalase, which optimize the storage and mobilization of sugars in a highly efficient manner. The ability of these insects to convert sugars into trehalose and glycogen, forms of stored energy, demonstrates a superior capacity for metabolic regulation compared to humans, whose systems are less adapted to prolonged high-sugar consumption [7]. Furthermore, the coordinated regulation of sugar metabolism at both the individual and colony levels in ants highlights innovative approaches to energy distribution that could inform human dietary interventions aiming to balance energy intake and expenditure. This coordination, which optimizes the use of available sugar resources, suggests a potential to mitigate metabolic stress. Their capacity to limit the accumulation of harmful metabolic byproducts, such as oxidative stress markers, also illustrates their evolutionary advantage in metabolic efficiency and offers translational insights into reducing oxidative damage and inflammation, two key contributors to diabetes complications.

The metabolic homeostasis achieved by these insects, despite high sugar exposure, sharply contrasts with the metabolic challenges faced by humans, who often experience insulin resistance, obesity, and type 2 diabetes in response to prolonged high-sugar diets. This ability is partly due to the unique fat body in insects, analogous to the human liver, which plays a pivotal role in managing energy storage and mobilization during metabolic stress. Additionally, the precision in hormonal regulation observed in insects, exemplified by the adipokinetic hormone (AKH), ensures tightly controlled energy mobilization. AKH stimulates the release of lipids and carbohydrates in response to environmental or physiological demands, showcasing a targeted approach to energy balance [31]. This contrasts with the more generalized and less efficient endocrine responses in humans, which are often insufficient to prevent metabolic dysfunction under conditions of dietary excess. Beyond hormonal control, social insects are capable of dynamically adjusting their metabolic pathways based on environmental sugar availability, a level of real-time metabolic flexibility that humans lack. This adaptability not only enables them to thrive in fluctuating dietary conditions but also underscores the potential for research to uncover how such mechanisms could be mimicked or adapted for human diabetes management. Their dual-pathway insulin signaling mechanisms further highlight their advanced metabolic systems. By separating critical signaling pathways, such as the MAPK pathway, they can avoid the metabolic bottlenecks that often lead to insulin resistance in humans, providing an evolutionary model of efficiency [32, 33].

Insects possess insulin-like peptides (ILPs) that perform functions analogous to human insulin, including regulating sugar uptake and storage, which positions them as valuable models for refining diabetes therapies. ILPs share structural and functional similarities with vertebrate insulin, making them promising candidates for bioengineering as therapeutic agents. The structural homology between ILPs and vertebrate insulin suggests the potential for designing alternative treatments characterized by improved specificity and fewer side effects compared to synthetic insulin analogs. These peptides also regulate behavioral responses such as foraging and energy conservation, signifying a highly integrated system of metabolic and behavioral regulation [34]. Applying these insights to human diabetes therapies could aid in managing the psychological aspects of diabetes, such as eating behaviors. Moreover, the hormonal regulators in insects, such as AKH and juvenile hormone (JH), complement ILP function by maintaining systemic energy homeostasis. This multitiered hormonal control demonstrates an advanced approach to managing metabolic efficiency that could inspire comprehensive diabetes treatment strategies in humans. Notably, dual-pathway insulin signaling mechanisms in insects have been shown to bypass common metabolic bottlenecks through alternative pathways, further underscoring the translational value of their metabolic innovations [33].

Genetic and epigenetic studies of bees and ants reveal crucial adaptations that contribute to their metabolic efficiency and resilience under dietary stress[35, 36]. Dual-pathway insulin signaling, suppressed or activated under different conditions, enables precise metabolic regulation, allowing them to adapt dynamically to varying nutrient availabilities [37–39]. This genetic flexibility indicates an evolutionarily refined mechanism for maintaining metabolic balance, which could inform targeted genetic therapies for diabetes in humans. The role of epigenetics in modulating metabolic pathways, especially under changing environmental conditions, highlights the importance of metabolic plasticity. By

fine-tuning gene expression in response to dietary imbalances, insects maintain homeostasis and prevent the onset of metabolic dysfunction. These insights suggest that epigenetic interventions could serve as preventive measures against insulin resistance in humans. Additionally, their genetic adaptations, which influence energy storage mechanisms like trehalose metabolism, provide valuable frameworks for investigating metabolic resilience. Translating these insights into human therapies could lead to novel solutions addressing the interplay of physiology and environmental factors that contribute to diabetes [32].

Insect-derived compounds, such as glycosaminoglycan (GbG) from field crickets, further demonstrate the therapeutic potential of insects for diabetes management. GbG has displayed significant antihyperglycemic effects in experimental models, including lowering blood glucose levels and enhancing the activity of antioxidant enzymes like catalase and superoxide dismutase [40–42]. These antioxidative properties mitigate oxidative stress, a critical factor in the progression of diabetes complications, thereby addressing aspects of the disease that are often insufficiently managed by current therapies. The multitarget activity of GbG, which simultaneously improves enzymatic activity and combats oxidative damage, exemplifies the potential for insect-derived compounds to address both the primary and secondary complications of diabetes. Developing bioengineered probiotics or supplements based on GbG could offer innovative and sustainable strategies for managing diabetes, particularly in low-resource settings where access to conventional treatments is limited [40].

The multitarget activity of plant-derived secondary metabolites, such as flavonoids, aligns with the complex nature of diabetes by addressing multiple molecular pathways simultaneously. Their interaction with key regulators like PPARs and their ability to improve glucose transport and reduce inflammation position them as effective agents for comprehensive diabetes management [43]. Moreover, flavonoids antioxidant properties protect against oxidative stress, further enhancing their therapeutic value. As preventive agents, flavonoids hold additional significance, as their dietary inclusion has been associated with a reduced risk of developing metabolic dysfunction. These compounds underscore nature's vast potential to provide bioactive molecules capable of addressing the multifactorial challenges posed by diabetes through more holistic and sustainable therapeutic approaches [30]. This exploration of natural compounds and strategies inspired by the metabolic adaptations of insects highlights a wealth of opportunities for advancing diabetes research and therapy.

Introduction of social insects as metabolic role models

Social insects such as bees and ants exhibit remarkable metabolic adaptations that allow them to thrive on high-sugar diets without developing the metabolic dysfunctions commonly observed in humans. This ability to maintain glucose homeostasis and precisely regulate energy utilization positions these insects as exceptional biological models for understanding metabolic resilience and exploring potential applications in human diabetes therapies. Differences in their sugar metabolism mechanisms compared to humans have profound implications for developing novel approaches to diabetes management, particularly as these insects demonstrate exceptional efficiency in processing and storing sugars while avoiding adverse effects like insulin resistance or glucose variability. These evolutionary adaptations offer a blueprint for advancing human metabolic health through translational research [44].

The reliance on trehalose as a central sugar molecule is a defining feature of metabolic regulation in bees and ants, enabling them to endure high-sugar diets with precision and stability. Trehalose serves not only as an energy source but also as a storage molecule, playing a critical role in the metabolic balance of these insects. Its storage and mobilization, facilitated by specialized mechanisms, prevent glucose fluctuations despite continuous sugar intake, a challenge which humans frequently encounter [45]. This disparity underlines the limitations of human glucose regulation when exposed to similar dietary conditions. In humans, prolonged high-sugar intake often leads to the onset of insulin resistance and metabolic dysregulation. The success of bees and ants in circumventing these issues underscores the evolutionary advantages provided by trehalose metabolism, which could inspire innovative strategies to enhance human metabolic stability.

A key factor contributing to the metabolic efficiency seen in bees and ants is the functional specialization of the fat body, an organ analogous to the human liver and adipose tissue. The fat body acts as a centralized hub for energy storage and regulation, enabling these insects to modulate energy distribution dynamically during fasting or periods of heightened energy demand [46]. In contrast, the human metabolic system often struggles to maintain such a fine-tuned balance, particularly during prolonged caloric surplus or deficit. The fat body's ability to prioritize energy allocation ensures these insects can sustain high metabolic activity without detrimental effects. Understanding and replicating these regulatory capabilities in humans could pave the way for therapies that improve metabolic resilience, especially under conditions of dietary excess.

The enzymatic pathways involved in sugar metabolism in bees are another essential aspect of their metabolic adaptations. Enzymes such as trehalose-6-phosphate synthase (TPS) play a pivotal role in synthesizing trehalose, which functions to stabilize glucose levels and optimize energy supply. This pathway provides bees with a consistent energy source while also preventing glucose imbalances [46]. The subsequent hydrolysis of trehalose into glucose by the enzyme trehalase exemplifies a highly regulated system of energy mobilization designed to meet immediate metabolic demands [47]. These mechanisms highlight the efficiency of sugar processing in bees, as opposed to the human reliance on insulin-driven pathways that are less adaptable to frequent glucose fluctuations. Translational research could explore enzyme-mimicking technologies to harness the benefits of trehalose metabolism for human diabetes management, potentially addressing persistent issues in glucose regulation [40].

Another significant aspect of metabolic regulation in social insects is the role of insulin-like peptides (ILPs), which share structural and functional similarities with human insulin. In bees and ants, ILPs are integral to maintaining energy homeostasis by regulating glucose uptake and storage [48]. These peptides also influence behavioral responses, such as feeding, linking metabolic and behavioral regulation in a highly coordinated manner. For humans, this dual functionality provides a compelling avenue for tackling diabetes-related metabolic and psychological challenges. While ILPs offer therapeutic potential, bridging the differences in receptor specificity and signaling cascades between insects and humans remains a significant challenge. Advanced genetic engineering and the development of peptide analogs tailored to human physiology could potentially overcome these barriers [33, 49].

Hormonal regulatory systems in social insects extend beyond ILPs and include critical hormones such as the adipokinetic hormone (AKH) and juvenile hormone (JH). AKH functions similarly to human glucagon, mobilizing stored trehalose and lipids in response to metabolic demands, thereby maintaining energy balance during fasting or activity [49]. This level of hormonal precision offers insights into enhancing glucose and lipid regulation in humans, where existing endocrine responses often fail to prevent metabolic dysfunction. Additionally, JH indirectly influences energy metabolism by regulating physiological processes such as development and reproduction, demonstrating the interconnectedness of hormonal systems in social insects. These insights into multifunctional hormonal roles could inform therapies targeting the hormonal imbalances prevalent in diabetes patients, emphasizing the need for integrated approaches to metabolic management [33].

The synergistic relationship between ILPs and AKH in sugar metabolism exemplifies the integrated hormonal systems of social insects. By coordinating metabolic and behavioral responses, these systems achieve tighter control over energy allocation. Humans, with their more generalized endocrine responses, lack this level of integration, making them more susceptible to metabolic dysfunction under dietary stress [33]. Translating this sophisticated hormonal regulation into human therapies could contribute to more precise glycemic and lipid control, addressing core challenges in diabetes management.

The genetic and epigenetic underpinnings of metabolic resilience in bees and ants further reveal their evolutionary adaptations to dietary stress. For instance, the dual-pathway insulin signaling observed in ants involves alternative routes, like the MAPK pathway, which bypass traditional insulin signaling bottlenecks such as the PI3 K/Akt pathway. This flexibility enables precise metabolic adjustments and provides a model for overcoming insulin resistance in humans [34]. Furthermore, gene-environment interactions, such as those modulated by the queen mandibular pheromone in bees, demonstrate the ability to enhance metabolic resilience through targeted genetic regulation [32]. Translational research could leverage these findings to develop genetic therapies aimed at improving metabolic plasticity in humans.

The ability of social insects to regulate energy storage and distribution dynamically, observed in ants at both individual and colony levels, underscores the role of specialized genetic adaptations in achieving systemic metabolic balance. For humans, mimicking this level of control could lead to therapies capable of addressing complex metabolic disorders, such as diabetes and obesity [50]. These genetic insights pave the way for targeted therapies that consider the interplay between gene expression and environmental factors, highlighting the potential for precision medicine approaches in diabetes care.

The evolutionary conserved nature of insulin-like pathways across species suggests that the metabolic efficiency of social insects can provide a biologically relevant framework for advancing human diabetes research. Despite the significant evolutionary gap, the adaptability of insect metabolic systems under dietary and environmental stressors offers valuable insights into creating more robust and flexible human metabolic therapies. The ability of social insects to thrive on carbohydrate-rich diets without metabolic dysregulation provides a compelling blueprint for addressing the multifactorial challenges of human diabetes [44]. Ethical and practical considerations must remain at the forefront of translating these insights

into therapies, ensuring that interdisciplinary collaboration guides the development of scalable and sustainable solutions for global diabetes care.

Metabolic adaptation of social insects

The exploration of the unique metabolic adaptations of social insects, like bees and ants, to their carbohydrate-rich diets provides a compelling foundation for developing novel therapeutic strategies for diabetes prevention and treatment in humans. Their ability to efficiently metabolize high-sugar diets, without succumbing to insulin resistance or related metabolic dysfunctions, offers significant biological insights that can inspire innovative approaches to addressing one of humankind's most pressing health challenges [44]. Unlike humans, bees and ants demonstrate a remarkable capacity to maintain metabolic balance despite consuming large amounts of simple sugars, such as glucose and sucrose. This ability underscores the potential of these insects as models for studying metabolic resilience and identifying alternative pathways for energy regulation that could address the underlying causes of diabetes. Leveraging these insights could pave the way for therapies that extend beyond glycemic control, aiming to mitigate metabolic dysfunction at its root.

The highly efficient sugar metabolism systems of bees and ants have evolved under very different environmental and dietary pressures compared to humans, enabling these insects to thrive on carbohydrate-rich diets with minimal risk of metabolic overload. Unlike humans, who often experience health complications such as obesity and diabetes in response to prolonged high-sugar intake, these insects exhibit tightly regulated sugar processing systems [33]. This contrast has significant implications for diabetes research, as it suggests the existence of metabolic strategies that humans either lack or underutilize. By studying the enzymatic, hormonal, and genetic systems in bees and ants, researchers can uncover novel therapeutic targets that mimic these insects metabolic precision. Investigating these mechanisms represents a critical departure from traditional pharmacological interventions, which often focus on singular aspects of glycemic control and fail to address the complex, multifactorial nature of diabetes [49].

One of the reasons for focusing on social insects is their exceptional ability to efficiently manage collective energy needs, which is achieved through metabolic systems finely tuned to support both individual health and the demands of the colony. Bees and ants live in highly organized social structures, where the energy requirements of the group are paramount. Their metabolic systems are not only robust but also adaptable, enabling them to effectively store and utilize energy even under fluctuating environmental conditions [44]. This ecological and biological significance makes them ideal subjects for understanding the coordination of energy metabolism at both macroscopic and microscopic levels. Translating these principles into human diabetes care could enhance metabolic resilience by developing therapies that address systemic energy imbalances rather than focusing solely on individual metabolic defects.

The metabolic efficiency exhibited by social insects offers a pathway toward precision medicine approaches for diabetes management, as their evolutionary adaptations point to alternative strategies for sugar utilization and storage. Bees and ants rely heavily on trehalose, a disaccharide that acts as both a storage molecule and a circulating sugar, demonstrating a metabolic stability absent in humans (Fig. 1). The enzymes involved in trehalose metabolism, such as trehalose-6-phosphate synthase (TPS) and trehalase, enable these insects to prevent glucose fluctuations while maintaining a consistent energy supply. This mechanism contrasts sharply with human physiology, where glucose variability is a central challenge in diabetes management. Mimicking such systems could lead to more effective control of glycemic levels and reduce the risk of long-term complications associated with persistent hyperglycemia [33, 44]. Moreover, the insights gained from studying these insects could contribute to more adaptable therapeutic approaches capable of addressing metabolic dysfunctions at their core.

The comparison between insect and human sugar metabolism highlights not only the evolutionary differences in energy regulation but also potential targets for therapeutic innovation. Whereas humans rely on glucose and glycogen as primary energy sources, bees and ants have evolved to utilize trehalose as a circulating sugar. This difference extends to the enzymatic pathways these organisms employ, with insects demonstrating a level of metabolic efficiency that outshines human systems. For example, the role of trehalose-6-phosphate synthase in catalyzing trehalose synthesis allows for precise sugar storage and utilization, whereas humans rely more heavily on insulin-driven pathways, which are less adaptable to constant dietary sugar intake. Understanding these enzymatic systems could trigger the development of novel therapies that optimize sugar transport and storage in humans, addressing key inefficiencies in current diabetes management practices [49].

The hormonal regulation of energy metabolism in bees and ants further underscores their metabolic sophistication, offering models for designing more effective diabetes therapies. Insulin-like peptides (ILPs) in these insects perform functions analogous to human insulin, including regulating sugar uptake and storage, but with a level of

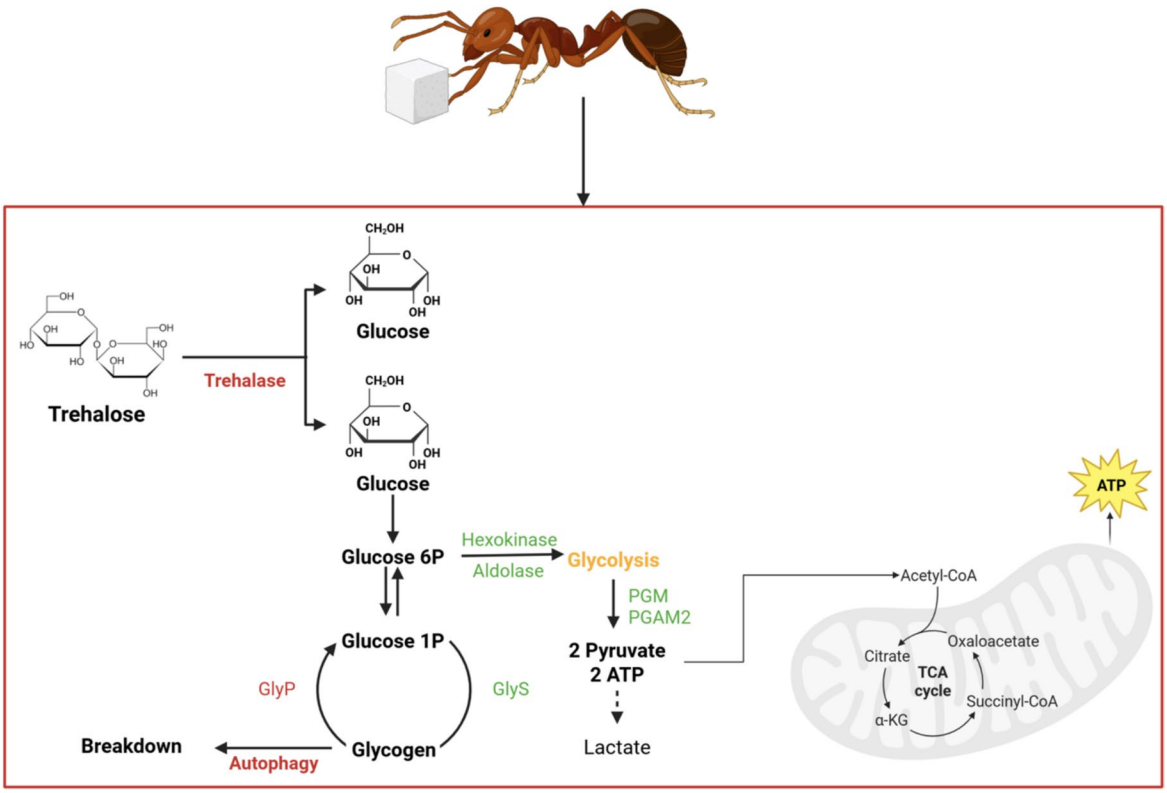

Fig. 1 Insect Trehalose-Based Energy Metabolism as a Blueprint for Metabolic Efficiency. This schematic illustrates the core metabolic pathway of trehalose utilization in ants, highlighting mechanisms that contribute to their metabolic resilience despite high sugar intake. Trehalose is hydrolyzed by *trehalase* into glucose, which is phosphorylated into glucose-6-phosphate (Glucose 6P) and further processed through glycolysis or stored as glycogen. Key enzymes such as *hexokinase*, *aldolase*, *PGM*, and *PGAM2* regulate glycolytic flux. Glycogen metabolism, including synthesis by *GlyS* and breakdown via *GlyP* and autophagy, maintains sugar homeostasis. Pyruvate generated from glycolysis enters the TCA cycle, producing ATP. While humans lack a trehalose-based metabolic system, this insect model demonstrates a tightly regulated energy buffering mechanism that could inspire future diabetes therapies, such as synthetic enzyme engineering or trehalose pathway mimetics for enhancing glycemic stability. This figure is not a proposal to replace glucose with trehalose in humans, but to showcase potential biochemical strategies to optimize glucose handling under metabolic stress

precision that is highly integrated with behavioral and environmental cues [33]. This dual functionality provides a fascinating blueprint for designing diabetes treatments that not only improve glycemic control but also address the psychological aspects of the disease, such as stress-induced eating behaviors. Additionally, the adipokinetic hormone (AKH), which functions similarly to human glucagon, facilitates energy mobilization during periods of intense activity or fasting. The absence of an equivalent system in humans represents a significant gap in metabolic regulation that could be addressed through bioengineering efforts aimed at replicating AKH-like functions to enhance metabolic flexibility [49]. Furthermore, the potential role of insect-derived bioactive components, such as those mimicking ILP mechanisms, could bridge the gap between behavioral interventions and physiological outcomes in diabetes management [51].

Genetic and epigenetic adaptations also play a vital role in the metabolic resilience observed in bees and ants, offering critical lessons for human diabetes research. These insects ability to dynamically adjust their genetic pathways in response to dietary variations highlights the importance of metabolic plasticity, a characteristic that is severely compromised in individuals with diabetes. For example, dual-pathway insulin signaling mechanisms in ants allow for greater metabolic flexibility bypassing traditional bottlenecks such as the PI3 K/Akt pathway, which is often implicated in human insulin resistance [33]. Such genetic insights could inform precision medicine approaches that aim to enhance metabolic adaptability in humans, potentially providing more sustainable solutions to managing diabetes under varying environmental and dietary conditions. Epigenetic factors, such as dietary influences on gene expression observed in insect fat bodies, can further offer insights into reprogramming human metabolism, indicating significant intersections between environmental inputs and genetic variability [49].

The translational potential of these findings is significant, but it is equally important to address the challenges and ethical considerations associated with adapting insect-derived metabolic strategies for human use. For instance, while trehalose metabolism represents a promising target for therapeutic innovation, its absence in humans necessitates the development of bioengineered systems capable of integrating this pathway without disrupting existing metabolic processes. This requires a multidisciplinary approach involving molecular biology, bioengineering, and clinical research to ensure that such interventions are both effective and safe [44]. Additionally, the societal acceptance of insect-based therapies must be carefully managed through educational initiatives that emphasize their scientific and health benefits. Ethical considerations, including the treatment of insects and the sustainability of large-scale farming practices, must also be prioritized to ensure these innovations align with global healthcare and ecological goals [52].

In summary, the metabolic adaptations of social insects, particularly those that enable them to thrive on high-sugar diets, offer a promising framework for developing novel diabetes therapies. By studying the enzymatic, hormonal, genetic, and epigenetic systems that underlie their metabolic efficiency, alternative pathways could be uncovered for managing glycemic control and addressing the root causes of metabolic dysfunction. The translational potential of these findings underscores the importance of integrating insights from entomology and biomedical science to advance diabetes care, paving the way for more holistic and sustainable therapeutic approaches.

Sugar diets of bees and ants

The remarkable ability of social insects to thrive on high-sugar diets without developing the metabolic dysfunctions seen in humans underscores the evolutionary *ingenuity* of their sugar processing systems. Through efficient dietary patterns, specialized enzymatic mechanisms, and physiological resilience, bees and ants exemplify how nature has optimized the energy utilization. This exploration reveals critical insights into their metabolic regulation, which can inform innovative therapeutic strategies for managing diabetes in humans. The following sections delve into the intricate dietary habits, enzymatic efficiencies, and physiological adaptations that make these insects a fascinating model for understanding and addressing the complexities of glucose metabolism.

Dietary patterns

The dietary patterns of social insects, namely bees and ants, represent a fascinating area of study, revealing their ability to maintain metabolic homeostasis despite consuming carbohydrate-rich diets (Fig. 2). These insects primarily rely on simple sugars like sucrose, glucose, and fructose, which are readily available from nectar, honeydew, and plant exudates. Unlike humans, who frequently encounter adverse metabolic effects with high-sugar diets, including insulin resistance and type 2 diabetes, bees and ants demonstrate evolutionary adaptations that allow them to process and utilize these sugars efficiently. This contrast not only highlights the metabolic resilience of social insects but also underscores the physiological limitations in humans that predispose them to sugar-related metabolic dysfunctions [44]. The ability of these insects to avoid the detrimental effects of prolonged sugar consumption raises critical questions about the underlying biochemical and regulatory mechanisms that could potentially be translated into human therapeutic approaches.

Social insects depend on dietary sugar not only to sustain individual energy needs but also to meet the demands of their colonies. The high-energy activities characteristic of bees and ants, such as foraging, hive-building, and reproduction, are fueled by the carbohydrates they ingest. Ants, for example, exhibit refined feeding behaviors, seeking sugar solutions with intermediate sucrose concentrations of approximately 13%. This preference likely reflects an adaptive mechanism to balance optimal energy intake while avoiding the detrimental effects of excessive sugar that might compromise metabolic efficiency [50]. The collective regulation of sugar intake at the colony level represents a sophisticated nutrient balancing system that optimizes carbohydrate acquisition and utilization. This level of behavioral and metabolic coordination offers unique insights into strategies that could mitigate energy imbalances in humans, whose metabolic responses to sugar-rich diets are comparatively rudimentary and often inadequate.

The diverse and role-specific dietary habits of bees and ants further illustrate their metabolic precision. Worker bees focus predominantly on collecting nectar to fulfill the hive's overall energy requirements, while forager ants modify their sugar consumption dynamically based on both environmental conditions and the colony's nutritional demands. This adaptability in sugar intake guarantees energy stability within the colony, even when external resources fluctuate [50]. Such flexibility in dietary patterns stands in stark contrast to human metabolic responses, where prolonged exposure to high-sugar diets can lead to significant health challenges, including obesity and metabolic syndrome. These role-specific dietary strategies in social insects highlight the importance of contextual energy management, which could inspire novel dietary interventions in humans aimed at achieving long-term metabolic balance.

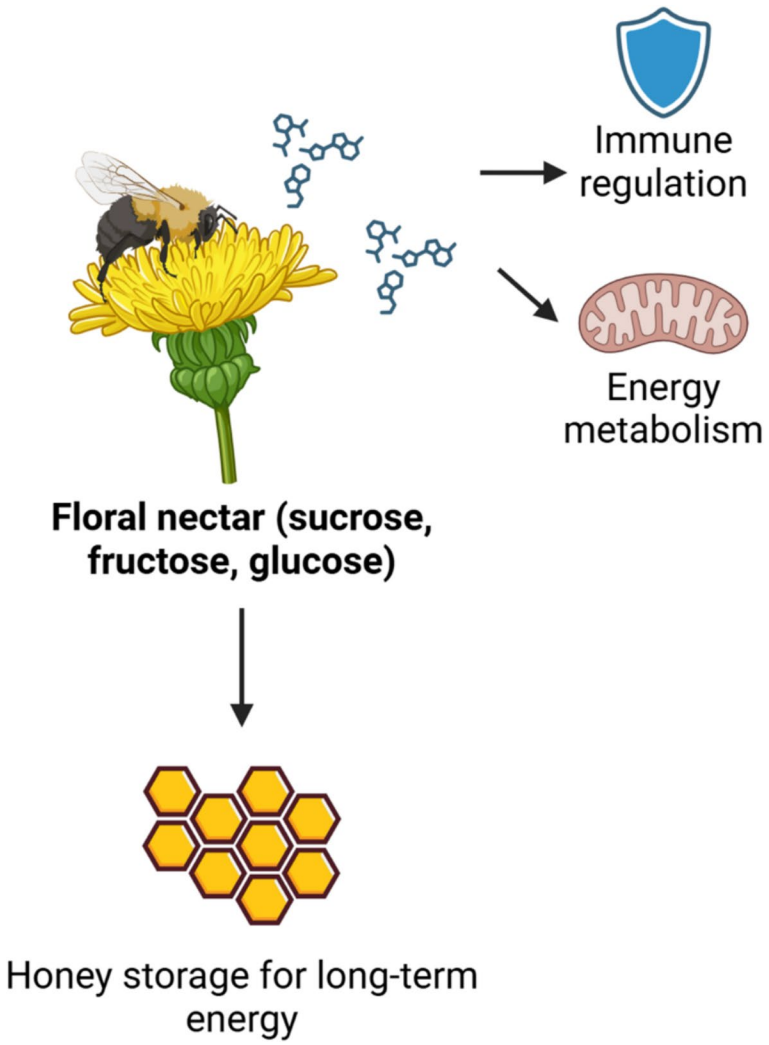

Fig. 2 Dietary pattern of Bee's. Illustration depicting bees collecting nectar rich in sucrose, fructose, and glucose from floral sources, and converting it into honey for long-term energy storage. The nectar also contains bioactive compounds involved in energy metabolism and immune regulation in bees

A critical component of sugar regulation in bees and ants is the fat body, an organ functionally analogous to the human liver and adipose tissue. This structure plays a central role in the storage and mobilization of energy. In these insects, glucose is primarily stored as trehalose and glycogen, both of which serve as crucial energy reserves. During periods of starvation or reduced sugar availability, the stored energy is systematically metabolized to sustain circulating sugar levels, ensuring continued survival and activity [46]. This mechanism acts as a highly efficient metabolic safeguard against energy deficits, a feature largely absent in humans without external dietary interventions. The metabolic stability provided by the fat body further emphasizes the evolutionary adaptations of social insects in maintaining homeostasis under varying dietary and environmental conditions. Exploring how these mechanisms might inform human metabolic therapies remains a promising area for further investigation.

Royal jelly exemplifies the influence of specialized diets on metabolic resilience and longevity, particularly in social insects like honeybees. This substance, consumed exclusively by queen bees, is rich in bioactive compounds such as royalactin and 10-hydroxydecenoic acid. These components are critical for the queen's reproductive capabilities while also contributing to her exceptional metabolic efficiency and significantly extended lifespan [53]. The unique nutritional properties of royal jelly underscore the profound impact of dietary composition on metabolic function. This finding raises interesting questions about whether specific bioactive compounds

in human diets could similarly enhance metabolic performance and promote resilience against metabolic disorders such as diabetes. Investigating the molecular properties of royal jelly and its potential translational applications could provide valuable insights into dietary-based approaches for metabolic health optimization.

Studies of silkworms, another sugar-consuming insect, offer additional parallels to the metabolic adaptations observed in bees and ants. Silkworms demonstrate an exceptional ability to process sucrose-rich diets by storing surplus sugar in their fat bodies without experiencing adverse effects. By contrast, humans exposed to excessive dietary sugar typically encounter metabolic complications such as insulin resistance and chronic inflammation. The metabolic efficiency observed in silkworms highlights evolutionary mechanisms that allow for effective sugar storage and utilization, which are absent in humans [54]. This comparison underscores the potential advantages of studying insect metabolic systems to uncover biochemical pathways that could be applied to improve human metabolic health. Although significant differences exist between human and insect physiology, the parallels in sugar metabolism suggest the possibility of developing targeted therapies or interventions aimed at enhancing energy storage and utilization pathways in humans.

The dietary adaptations of bees and ants provide a compelling model for studying metabolic efficiency and resilience. The precision with which these insects regulate sugar intake, storage, and utilization highlights evolutionary advantages that allow them to thrive under dietary conditions that would typically lead to metabolic dysfunction in humans. By examining these mechanisms in greater detail, researchers can gain valuable insights into potential therapeutic approaches for managing human metabolic diseases such as diabetes. The rich knowledge offered by these insects' dietary strategies serves as a foundation for future innovations in metabolic science and human health.

Efficient sugar processing

Efficient sugar metabolism in bees and ants is facilitated by specific enzymatic pathways that ensure precise energy storage and release. Two critical enzymes, trehalose-6-phosphate synthase (TPS) and trehalase, play a central role in this process. TPS catalyzes the formation of trehalose-6-phosphate, which is then converted into trehalose, a disaccharide that functions as a stable and mobilizable energy source. Trehalase hydrolyzes trehalose back into glucose when needed, enabling these insects to regulate energy metabolism with remarkable precision [46, 47]. This enzymatic cycle ensures that energy demands are met in a highly regulated manner, preventing potential imbalances that could disrupt metabolic stability. In contrast, humans lack a trehalose-based system, relying instead on insulin-regulated glucose metabolism, which often proves less effective in preventing conditions such as hyperglycemia or insulin resistance under high-sugar dietary stress. This absence in humans highlights a critical area for potential bioengineering research, seeking to replicate the efficiency of these enzymatic cycles in human metabolic systems [55].

One of the remarkable features of the trehalose-processing pathway is its ability to adapt enzymatic activity to the ecological and physiological demands of bees and ants. In insects like silkworms, consumption of high-sugar diets is associated with an increase in glycogen storage in the fat body. This adaptation is mediated by the activity of trehalose metabolic enzymes, demonstrating their role in buffering against sugar imbalances that might otherwise lead to metabolic dysfunction [46, 55]. This functional adaptation shows the plasticity of trehalose metabolism, which provides a metabolic safeguard under varying conditions. For humans, whose metabolic systems lack equivalent adaptive mechanisms, insights into these enzymatic pathways could inform novel therapeutic strategies, potentially involving engineered enzymes designed to improve energy buffering and storage in individuals with diabetes.

The fat body is a central metabolic hub in social insects, playing a pivotal role in their efficient sugar metabolism. This organ is functionally analogous to the human liver and adipose tissue, yet it integrates multiple metabolic roles within a single structure. It synthesizes and stores glycogen while mobilizing trehalose to maintain a steady supply of sugars during periods of fasting or high energy demand [46, 49]. This integration offers a level of efficiency that is absent in human systems, where the liver and adipose tissue operate in a more compartmentalized fashion. The metabolic stability provided by the fat body enables bees and ants to avoid fluctuations in circulating sugar levels, a challenge that remains a major issue in human diabetes management. Future research could explore whether integrating some aspects of this multifunctional metabolic regulation into human therapies might enhance metabolic resilience under dietary stress.

During energy-demanding activities such as flight, foraging, or colony-related tasks, the mobilization of stored energy in the fat body ensures stability in sugar levels. This regulation prevents metabolic fluctuations that could otherwise impair physiological function [49]. The mechanisms underlying this precise control highlight the physiological resilience of bees and ants to metabolic stress, providing a stark contrast to human systems, which are prone to imbalances under similar conditions. By understanding and mimicking these regulatory

pathways, particularly for addressing metabolic instability during fasting or physical exertion, human diabetes treatments could gain a new dimension of effectiveness.

In some scenarios, the regulation of fat body glycogen levels in insects can occur independently of hormonal signals. For instance, during periods of starvation, the fat body autonomously maintains circulating sugar levels, which serves as a safeguard against energy deficits [46]. This tissue-specific regulation has been observed in Drosophila, an insect model, where the ability to maintain metabolic balance without external hormonal cues provides remarkable resilience to environmental stress. In humans, however, the reliance on systemic hormonal control often leads to vulnerabilities, particularly under conditions of metabolic stress. Investigating tissue-specific regulatory mechanisms in insects could shed light on novel strategies for enhancing autonomous metabolic stability in humans.

The adipokinetic hormone (AKH), a counterpart to human glucagon, plays an essential role in orchestrating the mobilization of energy stores in response to metabolic demands. AKH activates pathways such as glycogenolysis and lipolysis, ensuring that carbohydrates and lipids are efficiently mobilized during periods of intense activity or fasting [47, 49]. This level of hormonal precision underscores its potential as a model for improving glucose and lipid regulation in humans, where existing endocrine responses often fail to prevent metabolic imbalances. The parallels between AKH and human glucagon also suggest opportunities for developing therapies that mimic this hormonal regulation to address insulin resistance and other metabolic challenges.

The genetic and physiological roles of AKH are well-demonstrated through studies of its receptor, AKHR. Mutations in either AKH or AKHR profoundly affect energy storage, leading to obesity-like phenotypes in Drosophila when AKH activity is disrupted and to reduced lipid reserves when it is overexpressed [49]. These findings reveal the tightly regulated balance of energy storage and mobilization mediated by AKH, and its potential translational relevance for addressing human metabolic disorders. Moreover, AKH enhances the activity of enzymes like trehalase, achieving a synchronized hormonal-enzymatic response that underscores the efficiency of insect energy regulation systems [47, 49]. This coupling represents an integrated metabolic mechanism that could inspire interventions aimed at improving glycemic control in humans.

Social insects also display complex behavioral adaptations to regulate sugar intake on both individual and collective levels. Ants, for instance, exhibit a preference for sucrose concentrations of around 13%, which represents an adaptive balance to optimize energy intake while preventing metabolic overload [50]. The regulation of sugar intake at a colony level, illustrated by dynamic foraging strategies, demonstrates a sophisticated system that prevents metabolic imbalances. For example, ants initially recruit more foragers to higher-quality food sources but reduce recruitment over time as energy needs are met. This behavioral regulation complements their physiological adaptations, providing new perspectives for strategies to mitigate energy imbalances in humans, who lack comparable regulatory behaviors in response to dietary sugar.

Nutrient balancing further demonstrates the adaptability of ants' sugar metabolism. When carbohydrate demands vary, such as during life stages with a higher presence of larvae in the colony, ants exhibit greater accuracy in sugar regulation [50]. This level of precision ensures systemic metabolic equilibrium without causing energy deficits or excesses. Combined with the efficiency of their fat body in synthesizing energy reserves like trehalose and glycogen, ants exemplify resilience to dietary changes. For humans, understanding how such precise nutrient balancing operates at both physiological and behavioral levels could inform new strategies for managing metabolic diseases.

Compounds derived from other insects, like cricket glycosaminoglycans (GbG), further highlight the potential of insect-derived biochemicals in addressing diabetes. GbG exhibits antioxidant properties that enhance the activity of key enzymes like catalase and superoxide dismutase, reducing oxidative damage in diabetic models [40]. These properties also lead to reductions in markers of diabetes such as blood glucose levels and protein carbonyl content, providing a multifaceted approach to promoting glycemic control and minimizing oxidative stress-related complications [40]. The multitarget activity of GbG underlines the broader applications of insect-based mechanisms in human diabetes treatments, offering holistic solutions to the multifactorial nature of the disease. Such findings pave the way for exploring the integration of insect-inspired pathways into human therapeutic approaches.

The enzymatic, hormonal, and behavioral mechanisms involved in sugar metabolism in social insects continue to provide an invaluable foundation for understanding metabolic efficiency. By investigating these integrated systems, researchers are better positioned to derive innovative approaches for improving metabolic resilience and glycemic regulation in humans.

Physiological resilience

Physiological resilience to metabolic stress in bees and ants is a result of their specialized sugar-processing systems, which prevent the accumulation of harmful

metabolic byproducts (Fig. 3). These insects have evolved mechanisms that allow them to efficiently utilize sugars as an energy source while avoiding the detrimental effects typically associated with high-sugar diets. A critical component of this resilience is the fat body, an organ that functions similarly to the liver and adipose tissue in humans. The fat body integrates multiple metabolic roles, including the synthesis and storage of glycogen and the mobilization of trehalose during energy-demanding conditions or periods of fasting. This dual functionality ensures metabolic stability, even under fluctuating dietary sugar intake [46, 49]. Unlike humans, who exhibit metabolic instability due to the compartmentalized functions of the liver and adipose tissue, the integrated approach of the fat body offers a model for enhanced metabolic efficiency. This raises critical questions about whether similar integration strategies could be applied to improve human metabolic responses, particularly in individuals with diabetes who struggle with maintaining blood glucose levels.

Hormonal regulation plays a pivotal role in the metabolic resilience of bees and ants. The adipokinetic hormone (AKH), which is functionally analogous to human glucagon, is central to energy balance in these organisms. AKH mobilizes carbohydrate and lipid reserves from the fat body in response to high energy demands, such as during foraging or flight. Research has shown that null mutations in AKH lead to obesity in Drosophila, while overexpression results in significantly reduced lipid reserves, demonstrating AKH's essential role in maintaining energy balance [49]. This hormonal precision highlights the potential for developing therapies inspired by AKH to mimic its regulatory effects in humans, particularly for addressing obesity and its associated metabolic complications. However, it remains crucial to investigate the broader systemic implications of AKH-inspired interventions, especially in a human context where endocrine responses are inherently more complex and influenced by a wide array of hormonal interactions.

The dietary adaptations of bees and ants further enhance their remarkable physiological resilience. For instance, royal jelly, a nutrient-dense secretion consumed exclusively by queen bees, contains bioactive compounds such as 10-hydroxydecenoic acid and royalactin that significantly improve metabolic efficiency and contribute to the queen's exceptional longevity [56]. These compounds increase her capacity to utilize dietary sugars without succumbing to metabolic stress, suggesting a direct

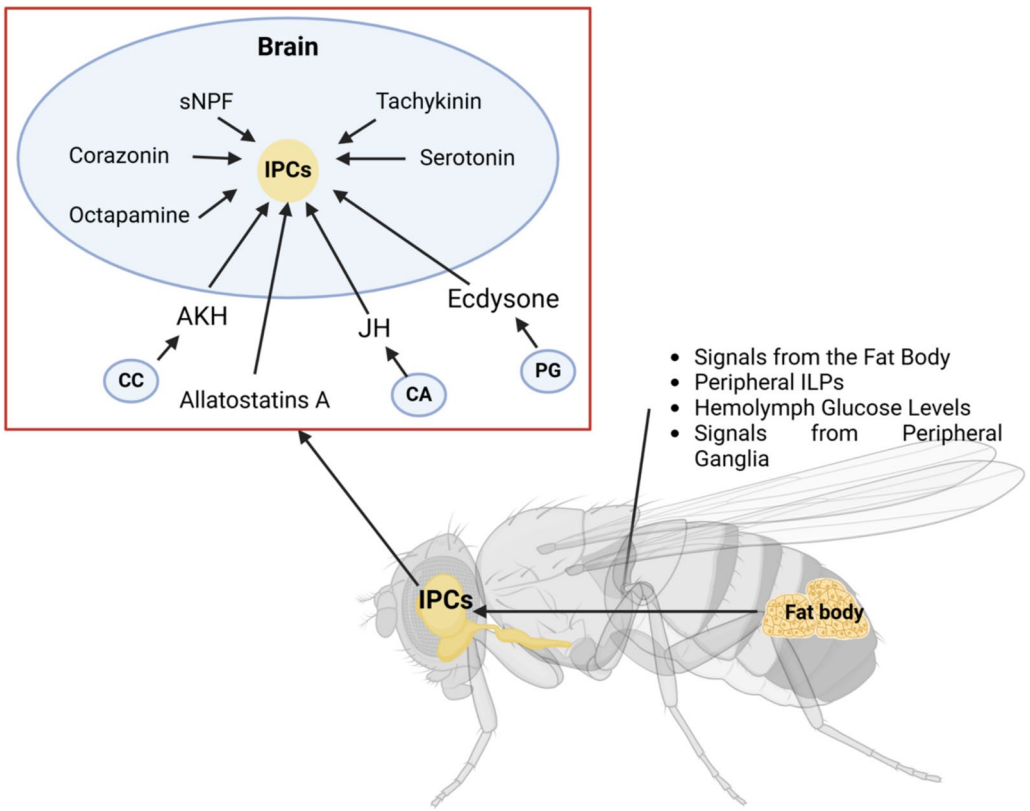

Fig. 3 Hormonal Regulation of Metabolism in Social Insects. Overview of the role insulin-like peptides (ILPs) and adipokinetic hormone (AKH) play in regulating energy storage and mobilization, highlighting their adaptive flexibility compared to human insulin and glucagon pathways

relationship between dietary composition and metabolic benefits [53, 57]. Exploring the molecular mechanisms of royal jelly's effects could inspire dietary interventions in humans aimed at optimizing metabolic functions. However, the translation of such compounds to human therapies requires careful investigation into dosage, bioavailability, and long-term effects. Moreover, the sustainability implications of sourcing royal jelly for large-scale therapeutic use warrant further consideration, given the ecological significance of honeybee populations.

Oxidative stress regulation is another critical factor contributing to the metabolic resilience of social insects. Cricket-derived glycosaminoglycans (GbG) exemplify the role of physiological adaptations in mitigating oxidative damage. These compounds enhance the activity of key antioxidant enzymes such as catalase, superoxide dismutase, and glutathione peroxidase, which collectively reduce oxidative damage in diabetic models [40]. This reduction in oxidative stress is particularly significant, as oxidative damage is a well-documented contributor to diabetic complications in humans. The ability of GbG to simultaneously lower blood glucose levels and decrease protein carbonyl content underscores its multitarget potential as a therapeutic agent. Translational efforts to incorporate similar antioxidant pathways into human treatments could offer a more holistic approach to managing diabetes, addressing not only glycemic control but also the systemic damage resulting from oxidative stress. Nonetheless, additional research is needed to elucidate the precise mechanisms by which GbG exerts its effects and to assess its safety and efficacy in human trials.

Genetic regulation represents another cornerstone of the metabolic resilience observed in bees and ants. Environmental and social factors, such as queen mandibular pheromone and vitellogenin (Vg), influence gene expression in bees, enabling stable lipid regulation even under variable dietary conditions. These gene-environment interactions highlight the importance of metabolic plasticity, a feature that is often compromised in individuals with diabetes [32]. For example, Vg plays a role in stabilizing lipid levels, ensuring that energy reserves are utilized efficiently without causing imbalances [58]. This genetic adaptability offers critical lessons for human diabetes research, particularly in the development of precision medicine approaches aimed at enhancing metabolic flexibility. However, the complexities of human metabolic pathways, which are subject to more diverse and interactive genetic and environmental influences, present a significant challenge to translating these mechanisms directly. Targeted gene-editing techniques, such as CRISPR, may provide a viable method for implementing similar genetic adaptations in humans, but ethical and technical considerations must first be addressed.

The regulation of insulin-like peptides (ILPs) in insects serves as an additional mechanism contributing to their resilience to metabolic stress. By tightly controlling sugar homeostasis, ILPs perform functions analogous to human insulin. Dietary interventions in Drosophila melanogaster, such as those involving sucrose-induced diabetes models, have demonstrated that the downregulation of ILP-2 and insulin receptor (InR), coupled with the upregulation of insulin-like growth factor binding protein L2 (Imp-L2), significantly improves glycemic control [33]. These findings highlight the potential of modulating insulin signaling pathways to enhance insulin sensitivity and promote metabolic resilience under high-sugar dietary conditions. However, the insect ILP system is more adaptive and integrated with environmental cues than human insulin pathways, which are prone to dysregulation in response to prolonged high-sugar intake. While these differences pose challenges to direct translation, they also provide opportunities for exploring novel approaches to insulin regulation that incorporate elements of adaptive, context-sensitive control.

The exceptional physiological resilience of bees and ants to metabolic stress underscores their potential as models for developing innovative approaches to managing human metabolic dysfunctions. By examining the enzymatic, hormonal, genetic, and dietary factors that contribute to their metabolic efficiency, researchers can gain valuable insights into alternative pathways for maintaining energy balance and preventing metabolic diseases like diabetes. These insights highlight the critical need for interdisciplinary research involving entomology, molecular biology, and clinical science to harness the full potential of these strategies for improving human metabolic health.

Unique mechanisms in sugar metabolism: bees and ants versus humans

Understanding the unique mechanisms of sugar metabolism in social insects such as bees and ants reveals profound insights that could inform innovative therapeutic strategies for diabetes management in humans. This exploration delves into the intricacies of metabolic regulation, highlighting key enzymatic systems, hormonal pathways, and genetic adaptations that enable these insects to thrive on high-sugar diets without developing metabolic dysfunctions (Table 1). By comparing these mechanisms to human physiology, the discussion uncovers opportunities for enhancing metabolic flexibility and resilience, paving the way for novel approaches to diabetes prevention and treatment. Through this comparative lens, the work sets the stage for a deeper exploration of how nature's solutions can address one of today's most pressing health challenges.

Table 1 Comparative overview of sugar metabolism strategies in social insects and humans

Aspect of metabolism	Bees and ants	Humans	Translational opportunities
Primary Sugar Molecule	Trehalose	Glucose	Engineering trehalose pathways for glucose stability
Energy Storage	Glycogen and Trehalose (Fat body)	Glycogen (Liver & muscle tissue)	Enhancing energy buffering through enzyme mimetics
Key Enzymes	Trehalose-6-phosphate synthase (TPS), Trehalase	Glycogen synthase, Glycogen phosphorylase	Synthetic enzyme engineering for enhanced glucose regulation
Hormonal Regulation	Insulin-like peptides (ILPs), Adipokinetic hormone (AKH)	Insulin, Glucagon	AKH analogs for better glycemic and lipid control
Genetic Regulation	Dual-pathway insulin signaling, Environmental adaptability	PI3 K/Akt insulin pathway predominance	Gene-editing (e.g., CRISPR) for insulin pathway flexibility
Oxidative Stress Management	Highly efficient antioxidant enzyme systems (e.g., cricket GbG)	Moderate endogenous antioxidant capacity	Bioactive antioxidant supplementation
Dietary Adaptability	Precise regulation of sugar intake based on colony needs	Limited behavioral regulation of sugar intake	Nutritional interventions mimicking colony nutrient balancing

Comparative metabolic regulation

Bees and ants exhibit remarkable efficiency in sugar metabolism, enabling them to thrive on high-sugar diets without succumbing to metabolic dysfunctions such as insulin resistance or type 2 diabetes mellitus (Fig. 4). This metabolic proficiency contrasts sharply with the human response to excessive sugar consumption, where prolonged dietary imbalances often result in adverse health outcomes. This distinction is deeply rooted in the evolutionary optimization of metabolic pathways in social insects, which confer resilience against glucose fluctuations and prevent the accumulation of harmful glucose or lipid byproducts. For example, mechanisms such as the synthesis, storage, and regulated release of energy reserves are finely tuned in these insects, ensuring metabolic homeostasis even under conditions of dietary stress [44, 55]. While these adaptations underscore the robustness of insect metabolism, they also highlight the comparative metabolic inflexibilities in humans. A critical research direction involves understanding whether elements of these pathways could be adapted or mimicked to enhance metabolic resilience in humans, particularly in light of the prevalence of diabetes-related complications.

A central feature of metabolic integration in bees and ants is the functionality of the fat body, an organ that combines the roles of glycogen synthesis, lipid mobilization, and sugar regulation within a single structure. This multifunctional organ, functionally analogous to the human liver and adipose tissue, demonstrates significantly greater integration of metabolic activities. This unique structural specialization ensures a continuous energy supply, allowing bees and ants to sustain energy-demanding activities even during fasting or dietary fluctuations [46, 49]. By comparison, the human metabolic system, which divides these functions across specialized but separate organs, lacks the same level of metabolic synchrony. This compartmentalization is often a contributing factor to metabolic imbalances in humans, particularly under conditions of dietary stress where coordination between the liver and adipose tissue may falter. The organization and function of the insect fat body not only represent an evolutionary advantage but also offer a potential model for designing therapeutic interventions aimed at improving metabolic regulation in humans.

Trehalose, a disaccharide found exclusively in insects, plays a pivotal role in their glucose regulation and represents another point of divergence from human metabolic systems. Trehalose is synthesized by the enzyme trehalose-6-phosphate synthase and catabolized by trehalase, creating a tightly regulated process for storing and mobilizing energy [47, 55]. This trehalose-based system provides bees and ants with remarkable glucose stability under conditions of both high energy demand and starvation, demonstrating its efficiency as an energy management strategy. By contrast, humans rely on glycogen stores and alternative metabolic pathways, which, while effective to an extent, are less adaptable and more prone to dysfunctions like insulin resistance when exposed to excessive sugar intake. The absence of a trehalose-based system in humans highlights a gap in metabolic resilience, raising questions about whether engineered metabolic innovations, such as trehalose-mimicking pathways, could enhance glucose regulation and energy buffering in human systems.

Hormonal regulation is another critical element that contributes to the metabolic efficiency observed in bees and ants. These insects rely on adipokinetic hormone (AKH), a glucagon-like peptide, to mobilize trehalose

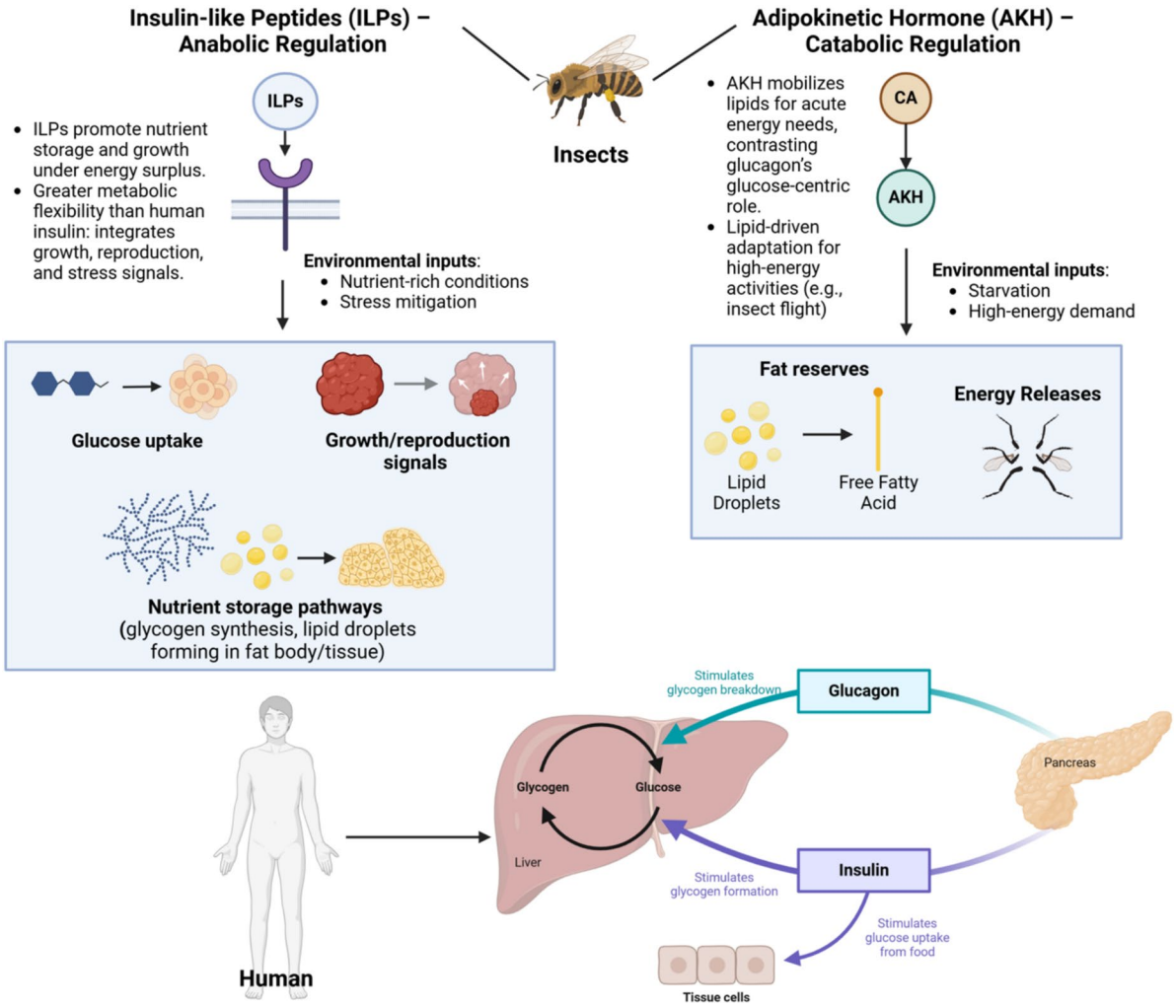

Fig. 4 Epigenetic and Genetic Adaptations in Bees and Ants. Depiction of genetic and epigenetic modifications that regulate metabolic enzyme activity and insulin sensitivity, enabling bees and ants to thrive in high-sugar environments without metabolic dysfunction

and lipid stores from the fat body during periods of high energy demand. Studies have demonstrated that null mutations in AKH pathways, such as in Drosophila, result in obesity, while overexpression leads to decreased lipid stores, indicating the fine balance maintained by this hormonal control system [49]. This stands in stark contrast to the human glucagon-insulin axis, which, while effective under normal conditions, often fails to prevent metabolic imbalances under chronic overnutrition or high-sugar diets. The precision of AKH-mediated regulation in insects offers a model for enhancing hormonal control mechanisms in humans, particularly in the context of addressing obesity and glucose dysregulation. However, adapting AKH-like pathways for human use would require careful evaluation of the long-term systemic impacts, given the complexities of the human endocrine system.

Genetic and epigenetic adaptations further enhance the metabolic resilience of bees and ants. These insects are equipped with mechanisms that modulate insulin-like peptides (ILPs), enabling them to optimize glucose use and storage in response to dietary conditions and energy demands. For instance, the suppression of ILPs under specific stressors allows for metabolic flexibility, providing an adaptive advantage that humans largely lack [48, 59]. Continuous overconsumption of sugar in humans disrupts the tight regulation of insulin pathways, often culminating in chronic diseases such as metabolic syndrome and diabetes. Insects, on the other hand, demonstrate an unparalleled ability to adjust their metabolic systems dynamically. This genetic plasticity underscores the potential for developing precision medicine approaches targeting similar pathways in humans. However, the challenges of directly translating these

mechanisms lie in the differences in physiological complexity and systemic interactions between humans and insects.

The structural and functional parallels between insect insulin-like peptides and human insulin present an intriguing potential for translational research. Both systems regulate sugar uptake and energy storage, yet insect mechanisms are more tightly integrated into behavioral feedback loops. For example, behavioral shifts such as reduced foraging activity following energy intake illustrate a direct link between metabolic status and external actions in insects [60]. This integration provides an additional layer of metabolic regulation, contrasting with human systems where behavioral and metabolic feedback loops are less pronounced [48, 55]. Investigating how these regulatory pathways operate in social insects may uncover novel strategies for improving glycemic control and metabolic efficiency in human therapies.

The metabolic strategies of bees and ants, characterized by their unique enzymatic systems, hormonal regulation, and genetic adaptations, provide a rich framework for understanding sugar metabolism. These insights offer a pathway for the development of innovative therapeutic strategies aimed at improving metabolic resilience in humans, particularly in the context of managing diabetes and related disorders. Recognizing the evolutionary advantages that underpin insect metabolic efficiency is a crucial step in exploring their translational potential for human health.

Key enzymatic systems and transporters

The sugar metabolism of bees and ants is supported by specialized enzymatic systems and transport mechanisms. One critical enzyme in this process is trehalose-6-phosphate synthase (TPS), which catalyzes the formation of trehalose-6-phosphate, subsequently converted into trehalose. Trehalose serves as a highly stable disaccharide that acts as the primary circulating sugar and energy reserve in many insects, including bees and ants [61]. This system allows these insects to manage energy demands and sustain glucose homeostasis effectively, even under fluctuating dietary conditions. In contrast, humans rely on glucose as the main circulating sugar, and their metabolic system lacks a comparable mechanism. This absence highlights the potential for translational applications, wherein TPS could be engineered into human metabolism to improve glucose storage and enhance the regulation of energy under varying dietary circumstances [46, 49]. While the stability of trehalose offers significant advantages, further research is required to determine its compatibility with the human metabolic network, which is inherently glucose-centered.

Trehalose-6-phosphate, formed through the TPS enzymatic pathway, also acts as a signaling molecule and a metabolic regulator. This intermediary compound optimizes sugar availability and utilization, granting bees and ants remarkable metabolic adaptability. Such precision, driven by TPS, underscores the efficiency of their metabolic regulation. Humans, on the other hand, exhibit a glucose-centric metabolic design that is more vulnerable to mismanagement, particularly under the strain of high-sugar diets. While initial studies suggest TPS-driven pathways could inspire innovations in human metabolic therapies, there are challenges in replicating the same level of adaptability due to the fundamental differences in human and insect sugar metabolism [46]. Research should investigate whether introducing trehalose-6-phosphate directly, or utilizing synthetic analogs, could enhance human metabolic processes without interfering with existing glucose-regulation mechanisms.

Trehalose stands out as a superior system for energy storage compared to glycogen, the primary glucose storage molecule in humans. The evolution of trehalose storage in insects reduces the likelihood of metabolic imbalances such as hyperglycemia or hypoglycemia that are common in human metabolic disorders. The translational application of trehalose-based systems in humans could revolutionize glucose regulation, particularly in diabetes management. For example, bioengineering pathways to mimic trehalose storage and utilization may provide a robust buffer against sudden changes in sugar intake and energy demand [49]. However, the challenge lies in integrating such a system into human physiology without disrupting the intricate balance of the current glucose-centric metabolic processes.

The enzyme trehalase is integral to the efficient metabolism of trehalose in bees and ants. Trehalase hydrolyzes trehalose back into glucose, facilitating a controlled and precise release of glucose during high-energy demand periods. This ensures a steady and continuous energy supply without overwhelming cellular systems. Such enzymatic efficiency enables insects to maintain metabolic equilibrium even with prolonged access to high-sugar diets. In comparison, human sugar metabolism often struggles with glucose level fluctuations, leading to conditions such as insulin resistance and type 2 diabetes mellitus. The absence of trehalase in humans presents an opportunity to explore the enzyme's potential through bioengineering. Whether through gene-editing technologies like CRISPR or enzyme supplementation, introducing trehalase could stabilize glucose levels and address the inefficiencies associated with hyperglycemia [46, 47, 55]. However, long-term implications on other metabolic pathways and the immune response to enzyme addition require thorough investigation.

The absence of trehalase in humans also limits their metabolic flexibility, as they cannot utilize trehalose as an energy reservoir. This limitation further highlights the disparity between insect and human metabolic systems. Introducing trehalase through advanced genetic engineering or enzymatic therapies could address this gap, allowing for greater energy buffering and stability in individuals living with diabetes. However, such interventions must account for the potential risks, including the disruption of existing metabolic pathways and immune responses to introduced enzymes. Comprehensive research is needed to evaluate the feasibility and safety of creating a human-equivalent trehalose metabolism system [40].

Although humans and insects utilize glucose transporters (GLUT) to maintain cellular glucose uptake, the intricate functionality of GLUT homologs in bees and ants is notably advanced. These transporters complement the efficiency of enzymatic pathways like those involving TPS and trehalase, enabling precise sugar mobilization tailored to environmental sugar availability and energy demands. This adaptability is particularly evident in ants, where GLUT homolog regulatory mechanisms provide metabolic resilience beyond the capabilities of humans. Studying these mechanisms could reveal therapeutic targets for improving cellular glucose uptake and reducing postprandial glucose spikes in humans with diabetes [49]. Nonetheless, the complexity of human GLUT systems necessitates careful integration of insect-inspired adaptations to ensure compatibility without unintended consequences.

Human GLUT systems primarily facilitate glucose entry into cells, but insect GLUT homologs exhibit nuanced regulatory capacities. These differences could inspire advancements in glycemic control technologies. For instance, developing synthetic GLUT variants modeled after insect systems may lead to therapies that enhance intracellular glucose regulation and reduce metabolic disruptions. However, translating such insights into applicable treatments will require extensive preclinical research to address potential systemic effects on human endocrine and metabolic networks [49].

A key distinction between insect and human metabolic systems lies in the structural and functional organization of their energy storage tissues. Bees and ants possess a centralized metabolic hub called the fat body, which integrates glycogen synthesis, lipid storage, and sugar regulation within a single structure. This unified approach increases metabolic efficiency and minimizes delays in energy mobilization, allowing these insects to sustain activity during fasting or sudden energy demands. In humans, the division of these functions between the liver and adipose tissue creates a more compartmentalized system often prone to miscoordination under metabolic stress. Adapting certain features of the insect fat body into human biology could optimize energy distribution and enhance resilience to metabolic imbalances, particularly in the diabetes context [46, 49]. However, replicating this organ's unified functionality in humans is a significant scientific challenge, requiring innovations in tissue engineering and synthetic biology.

The fat body's ability to buffer against sugar imbalances during dietary stress is an additional feature worth exploring. By efficiently synthesizing and storing glycogen in high-sugar conditions, insects avoid the metabolic disturbances commonly observed in humans. This capability highlights the potential for therapies targeting glycogen dynamics as a means to improve glucose homeostasis in diabetes management. Whether through pharmacological agents that replicate the metabolic properties of the fat body or through gene-editing strategies that enhance glycogen storage in human tissues, this approach offers promising avenues for therapeutic innovation [46].

The interplay between enzymes like TPS and trehalase and hormonal regulators such as adipokinetic hormone (AKH) exemplifies the efficiency and integration of insect sugar metabolism. AKH triggers the enzymatic release of glucose from trehalose, ensuring that energy demands are met in real time without compromising systemic metabolic balance. This tight regulation, absent in humans, emphasizes the potential for developing advanced diabetes treatments that achieve similar coordination between hormonal and enzymatic pathways [33, 49]. However, translating this synergy into human therapies will require significant research into how hormonal and enzymatic interactions can be harmonized within the human metabolic framework.

The absence of such integrated systems in humans underscores the potential for novel therapeutic pathways inspired by insects. Mimicking the coordinated activity of AKH and trehalase, for example, could lead to improvements in glucose regulation and energy distribution in diabetic patients. Yet, the challenges of replicating these mechanisms in the more complex and distinct human endocrine environment must not be underestimated. It is critical to evaluate the long-term viability and safety of introducing such integrated metabolic interventions [33, 49].

Research on diabetic silkworms has revealed that prolonged exposure to high-glucose diets results in increased glycogen storage in the fat body, demonstrating the adaptability of insect enzymatic pathways to sugar challenges [62, 63]. This finding highlights the robustness of their metabolic systems and their ability to mitigate sugar-induced stress. For humans, understanding

and replicating this adaptability could inspire therapeutic approaches to restore or improve glycogen balance, particularly in the context of hyperglycemia and related complications [55]. A detailed exploration of the regulatory mechanisms governing this response in silkworm models could inform the design of interventions tailored to human glycogen dynamics.

The coordinated action of TPS and trehalase in managing sugar uptake and storage underscores the robustness of insect metabolic systems. This functionality offers a model for engineering improved glycemic control strategies for individuals with diabetes, particularly those struggling with hyperglycemia or insulin resistance. Translating these findings into human applications presents a unique opportunity to bridge evolutionary metabolic efficiency and modern clinical needs [64]. Careful studies are essential to evaluate the feasibility and ethical considerations of implementing these systems in humans to minimize the risk of unintended side effects.

The adaptability of insect enzymatic systems to dietary sugar imbalances signals a broader translational potential in human diabetes management. By designing treatments inspired by these adaptive capabilities, researchers could address limitations in current therapies and provide more robust solutions to glycemic control. However, the challenges of integrating such systems into the human body necessitate interdisciplinary collaboration and extensive testing [55]. This exploration into enzymatic systems and transporters in bees and ants lays a strong foundation for advancing therapeutic research aimed at enhancing metabolic resilience in humans.

Hormonal regulation of energy metabolism

The hormonal regulation of energy metabolism in insects reveals a series of highly precise and integrated mechanisms that maintain metabolic homeostasis. These mechanisms, which include insulin-like peptides (ILPs), adipokinetic hormones (AKHs), and neuropeptide F (NPF), demonstrate the sophisticated interplay between hormonal signaling, nutrient processing, and metabolic flexibility. By examining these systems, valuable insights can be gained for advancing human diabetes research and therapeutic strategies.

Insulin-like peptides (ILPs) play a crucial role in regulating sugar metabolism in insects, acting as functional analogs to human insulin. In response to food intake, circulating ILPs suppress neuropeptides such as short neuropeptide F (sNPF), reducing sensitivity to food cues and search behaviors [65, 66]. This feedback mechanism creates an efficient alignment between energy intake and metabolic requirements. For example, in *Drosophila melanogaster*, ILPs released after food consumption directly inhibit sNPF expression in olfactory sensory neurons, curbing the drive for additional food [67]. This process ensures energy conservation and resource optimization. Such direct regulatory loops, linking metabolic needs with behavioral responses, starkly contrast with human systems, where insulin largely focuses on glucose uptake and storage, offering minimal impact on food-seeking behaviors. The absence of behaviorally integrated feedback in humans underscores the evolutionary divergence between species and the potential for harnessing insect ILP mechanisms to design human interventions that concurrently regulate glucose levels and appetite control [34].

In addition to their impact on behavior, ILPs regulate lipid and carbohydrate metabolism, providing robust layers of homeostatic control in insects. This alignment of energy regulation across multiple metabolic pathways is absent in human systems, where disruptions in glucose metabolism often lead to downstream imbalances in lipid processing. The tight coordination exhibited by ILPs offers a blueprint for designing holistic therapies that address multiple facets of metabolic dysfunction in diabetes. Furthermore, the conservation of ILP functions across diverse insect species underlines the evolutionary advantages of these mechanisms, suggesting their potential applicability in human metabolic research [34].

Adipokinetic hormones (AKHs) are another critical component of insect energy regulation, functioning as glucagon-like peptides that mobilize energy reserves during periods of demand. AKH stimulates the release of trehalose and lipid stores from the fat body, activating enzymes responsible for carbohydrate and lipid mobilization. This system mirrors the role of glucagon in humans but exhibits significantly greater efficiency and precision. For instance, null mutations in AKH or its receptor (AKHR) in *Drosophila* result in excessive adiposity due to impaired energy mobilization, while overexpression leads to reduced lipid reserves, underscoring the hormone's centrality in maintaining metabolic balance [68, 69]. AKH-like pathways could provide a framework for developing therapies to improve glucose regulation and mitigate excessive fat storage in humans with obesity and type 2 diabetes. However, the complexities of the human endocrine system necessitate careful evaluation of how AKH's regulatory actions could be integrated without disrupting existing hormonal interactions [49, 70].

Beyond its role in glucose and lipid metabolism, AKH is also involved in oxidative stress regulation. By activating antioxidant enzymes such as catalase and glutathione-S-transferase, AKH reduces oxidative stress biomarkers, such as protein carbonylation, in insect models. This dual functionality highlights its potential as both a metabolic and protective agent, addressing two major contributors to diabetes complications simultaneously. For individuals

with diabetes, oxidative damage is a significant factor in the progression of neuropathy, nephropathy, and retinopathy. AKH-based interventions that bolster antioxidant defenses could therefore offer a novel approach to mitigating these chronic complications. Nevertheless, translating AKH into human therapies requires extensive research to address questions regarding dosage, delivery mechanisms, and the long-term systemic effects of integrating insect-derived hormonal functions [70].

The dual-pathway insulin signaling observed in some social insects, such as *Harpegnathos saltator* ants, further underscores the evolutionary adaptations of insect energy regulation. In these ants, brain-produced ILPs specifically activate the MAPK pathway within the fat body and ovaries while bypassing the PI3 K/Akt pathway typically associated with insulin signaling in vertebrates [34]. This alternative signaling route enhances metabolic flexibility and supports energy storage and reproductive functions under varying dietary conditions. Humans rely predominantly on the PI3 K/Akt pathway for insulin-mediated glucose uptake, yet this pathway's dysfunction is a hallmark of insulin resistance and type 2 diabetes. The MAPK pathway's selective activation in ants provides a compelling alternative for modulating human insulin pathways. Designing therapies that target alternative insulin signaling routes, inspired by the insect MAPK activation strategy, may help overcome bottlenecks in human insulin receptor signaling and improve metabolic resilience. However, such strategies must be approached cautiously, given the potential for unanticipated impacts on the broader network of human endocrine regulation [34].

Neuropeptide F (NPF), the insect homolog of neuropeptide Y in humans, plays an integral role in nutrient signaling and energy storage. In *Drosophila*, midgut-derived NPF regulates systemic energy balance by preventing excessive triglyceride accumulation and maintaining glucose and trehalose concentrations [71]. Genetic knockdown of NPF results in reduced triglyceride levels and altered glucose metabolism, demonstrating its dual role in sugar and lipid homeostasis. The opposing functions of brain-derived and midgut-derived NPF in governing food intake and energy storage illustrate the complexity of insect nutrient signaling. This sophisticated regulatory network could serve as a model for addressing human metabolic disorders, as it balances nutrient availability with metabolic demands. Additionally, NPF's ability to influence metabolites of the tricarboxylic acid (TCA) cycle, such as fumarate and malate, further highlights its systemic impact on cellular energy metabolism. These findings suggest opportunities to explore neuropeptide Y and its pathways in human diabetes research, with the aim of designing therapies that target the intersection of glucose, lipid, and mitochondrial function [72].

Insect models also offer valuable insights into the effects of prolonged high-glucose diets, particularly in the context of diabetes research. Diabetic silkworm studies reveal significant parallels with human metabolic responses. For example, the consumption of high-glucose diets by silkworms leads to increased sugar levels in the hemolymph and hyperlipidemic phenotypes, resembling lipid dysregulation in humans with diabetes. The ability of human insulin administration to normalize these sugar levels highlights structural and functional similarities between insect insulin pathways and their human counterparts. This finding supports the potential utility of insect models in testing and refining human insulin therapies. Additionally, therapeutic agents like metformin and pioglitazone have demonstrated efficacy in improving glucose tolerance in diabetic silkworms, reinforcing the relevance of these models for evaluating human-targeted diabetes treatments. However, while these parallels are promising, the metabolic differences between insects and humans necessitate cautious interpretation of results, particularly when extrapolating findings to human clinical contexts [55].

The insights gained from hormonal regulation in insects emphasize the complexity and precision of their metabolic systems. These mechanisms, which integrate behavioral, metabolic, and stress-response pathways, offer a wealth of possibilities for advancing human diabetes research. However, significant challenges remain in translating these findings into therapies, given the fundamental physiological and systemic differences between insects and humans. Further interdisciplinary research is critical to explore how these intricate hormonal systems can inform innovative approaches to metabolic health in humans.

Genetic and epigenetic adaptations

Bees and ants demonstrate remarkable genetic adaptations that enable precise regulation of metabolic pathways, particularly in managing high-sugar diets without succumbing to metabolic stress. One such adaptation involves the suppression of insulin-like peptides (ILPs) under specific dietary conditions [73, 74]. This suppression allows for greater metabolic flexibility, ensuring optimal energy distribution and avoiding the overload of metabolic systems. Evolutionarily optimized feedback mechanisms regulate this suppression, making it highly efficient and targeted. In humans, chronic overactivation of insulin pathways due to high sugar intake often leads to insulin resistance and metabolic imbalances, which are key hallmarks of type 2 diabetes. The ability of bees and ants to fine-tune ILP activity offers a potential

model for designing precision treatments for humans. Targeting insulin signaling pathways to mimic the selective suppression observed in these insects could provide new strategies for managing hyperglycemia and other metabolic dysfunctions. However, translating this insect-inspired mechanism to human therapies raises significant challenges, particularly due to the complexity of human endocrine regulation and the broader physiological impacts of modifying insulin activity. The development of such therapies would require extensive investigation to ensure targeted improvements without unintended systemic side effects.

Epigenetic modifications in bees also play a critical role in maintaining metabolic stability, even under varying environmental and dietary conditions. For example, the fat body—a multifunctional organ crucial for energy storage and metabolism—adjusts its gene expression in response to social and environmental cues such as queen mandibular pheromone and the protein vitellogenin (Vg) [59, 75]. Vitellogenin not only regulates lipid metabolism but also enhances oxidative stress resilience, ensuring that energy storage and mobilization are finely tuned [76]. This adaptability underscores the influence of social organization and environmental factors on metabolic regulation in bees. Translating such mechanisms into human therapeutic strategies could pave the way for innovative approaches to achieve metabolic stability and resilience against dietary-induced stress. For instance, developing agents that mimic the epigenetic regulatory effects of vitellogenin might improve lipid handling and oxidative stress management in individuals with metabolic disorders. Nevertheless, implementing epigenetic therapies introduces ethical and technical challenges, as these interventions may have long-term consequences that are difficult to predict. Research by Ament et al. highlights the critical role of vitellogenin in modulating energy storage and antioxidant responses, underscoring its therapeutic potential.

Research on ants reveals another intriguing adaptation in the form of dual-pathway insulin signaling, which provides metabolic flexibility and resilience. Unlike humans, who primarily rely on the PI3 K/Akt pathway for insulin-mediated glucose regulation, certain ant species such as *Harpegnathos saltator* activate an alternative MAPK pathway through brain-derived ILPs [77]. This diversification enables metabolic redundancy and allows ants to adapt their glucose regulation strategies to varying dietary and energy demands. The MAPK pathway also supports critical functions like energy storage and reproduction, which are particularly important for survival in social species. In humans, the predominance of the PI3 K/Akt pathway makes insulin signaling vulnerable to dysfunction, as seen in insulin resistance and type 2 diabetes. Inspired by ants, scientists could explore strategies to enhance or bypass the PI3 K/Akt pathway in favor of alternative mechanisms like MAPK signaling. While such approaches hold promise for improving metabolic resilience, the fundamental differences in endocrine complexity between humans and ants necessitate thorough investigations to assess the feasibility and potential risks of employing dual-pathway strategies in human treatments. Toprak's work on peptide hormones in insects provides further insights into how these signaling pathways contribute to lipid and carbohydrate mobilization, highlighting the broader implications for metabolic regulatory mechanisms [49].

The regulatory capacity of metabolic gene expression is another area where insects, such as *Drosophila melanogaster*, offer valuable insights. When challenged with high-sugar diets, *Drosophila* demonstrates tightly controlled expression of key metabolic genes, including the downregulation of ILP-2 and the insulin receptor (InR) as well as the upregulation of insulin-like growth factor binding protein Imp-L2 [78]. These genetic adjustments enhance glycemic control and maintain metabolic equilibrium, even under conditions that would typically induce stress in humans. Genetic interventions mimicking this regulatory precision could offer new ways to manage glucose homeostasis in humans. Utilizing gene-editing technologies such as CRISPR, researchers could potentially engineer similar regulatory capabilities into human metabolic pathways. Saliu and colleagues have demonstrated that dietary interventions with *Artocarpus camansi* in *Drosophila melanogaster* effectively modulate ILP-2 and Imp-L2 gene expression to restore glycemic control in high-sucrose conditions [33]. Their findings underscore the practical implications of these mechanisms in designing nutraceuticals with antihyperglycemic properties. However, translating these mechanisms into a human context raises questions about how such interventions would interact with the broader genetic network and whether they could maintain stability under the multifaceted demands of human physiology. Further research is needed to identify the specific elements of insect gene regulation that can be adapted without compromising human metabolic health.

Another key adaptation lies in the genetic encoding of enzymes involved in trehalose metabolism, particularly trehalose-6-phosphate synthase (TPS). Bees and ants rely on trehalose as a stable, energy-efficient circulating sugar, which provides metabolic advantages over the glycogen-based system predominant in humans [79]. Trehalose allows these insects to effectively store and mobilize energy, minimizing the risk of metabolic disturbances such as those associated with hyperglycemia or hypoglycemia. The potential introduction of trehalose-based

pathways into human metabolism through bioengineering could revolutionize glycemic control, especially in diabetes management. However, such an approach would require extensive research to ensure compatibility with human metabolic processes, which are inherently glucose-centered. Integrating trehalose-based systems into human physiology poses significant challenges related to enzyme functionality, immune responses, and long-term safety. Toprak highlights the centrality of trehalose metabolism in insect resilience to dietary sugar fluctuations, particularly through its role in energy buffering [49]. Despite these obstacles, the efficiency of trehalose metabolism offers a compelling avenue for developing innovative therapies to enhance metabolic resilience.

Epigenetic modulation by plant-derived compounds, such as curcumin, has been found to influence gene expression associated with metabolic pathways, drawing parallels with the adaptive mechanisms observed in social insects. Curcumin has demonstrated the ability to mimic some regulatory effects seen in bees and ants, such as improving oxidative stress resilience and enhancing lipid metabolism [80]. Kotha and Luthria's research emphasizes the diverse biological activities of curcumin, including its antioxidant properties, which could support metabolic regulation in humans [81]. Leveraging natural compounds like curcumin to induce beneficial epigenetic changes in humans could represent an interdisciplinary approach to addressing metabolic disorders. However, current research into the therapeutic potential of curcumin and similar compounds remains largely preliminary. Future studies should focus on elucidating the molecular mechanisms by which these compounds exert their effects and determining their long-term implications for human health. Additionally, integrating such compounds into diabetes management would require careful consideration of dosage, bioavailability, and potential interactions with existing medications.

The genetic and epigenetic adaptations of bees and ants provide a fascinating blueprint for improving human metabolic health. These insects exhibit sophisticated mechanisms for regulating sugar metabolism, enhancing metabolic flexibility, and maintaining homeostasis under challenging conditions (Fig. 5). While the translational potential of these adaptations is significant, their application to human therapies demands meticulous research, interdisciplinary collaboration, and ethical consideration to ensure safety and efficacy. Exploring these evolutionary strategies further could open new frontiers in the prevention and treatment of diabetes.

Translating insect metabolic insights to human diabetes prevention and treatment

As the global burden of diabetes continues to escalate, innovative approaches inspired by the metabolic strategies of social insects present promising avenues for prevention and treatment. This section explores the parallels

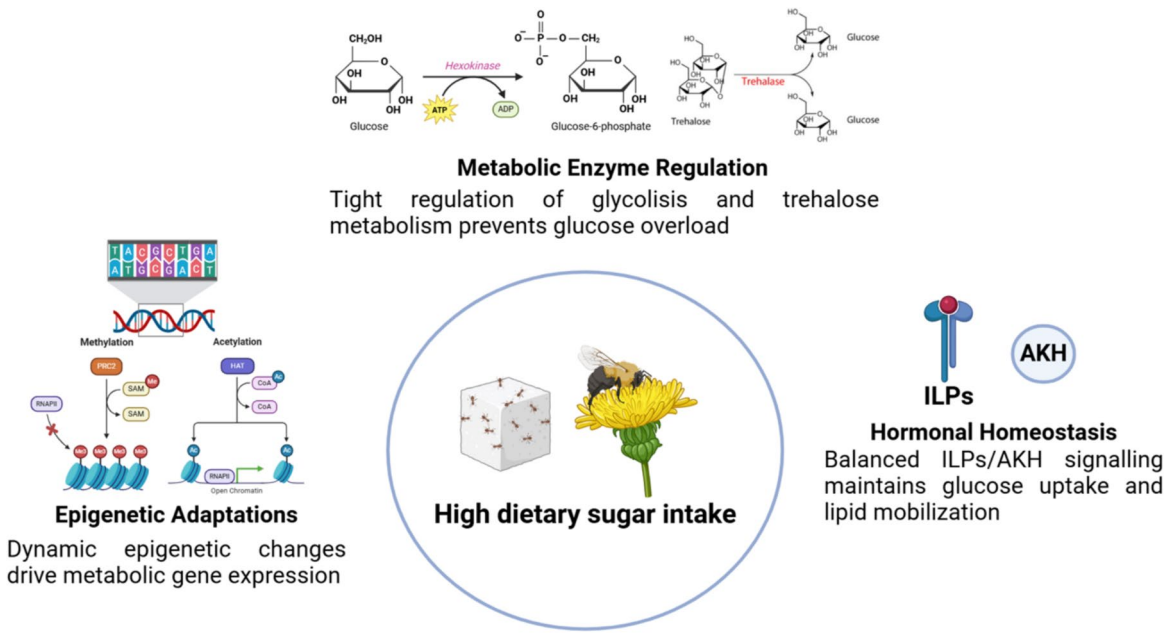

Fig. 5 Key Enzymes and Transporters in Ant and Bee Sugar Metabolism. Schematic representation of specialized enzymes including trehalose-6-phosphate synthase (TPS), trehalase, and glucose transporters (GLUTs), illustrating how social insects efficiently manage sugar conversion, storage, and mobilization without causing glucose toxicity

in hormonal and genetic pathways, enzymatic innovations, and bioengineering opportunities derived from insects, ultimately aiming to enhance human metabolic flexibility and resilience. By leveraging insights from the unique adaptations of bees and ants, practical solutions for diabetes management can emerge, addressing multifaceted challenges in the fight against this pervasive health crisis. The following discussions will delve into strategies that could revolutionize current paradigms in diabetes care and improve health outcomes for diverse populations.

Hormonal and genetic pathway parallels

The study of hormonal and genetic pathway parallels between insects and humans offers a promising avenue for understanding and addressing the complexities of diabetes management. Insulin-like peptides (ILPs) found in insects, such as bees and ants, exhibit structural and functional homology with human insulin, providing opportunities to investigate their application in human diabetes treatment. In insects, ILPs regulate sugar metabolism by promoting glucose uptake and energy storage, akin to human insulin, but they possess distinct mechanisms that enhance energy efficiency and metabolic resilience [82]. These peptides not only maintain glucose homeostasis but also integrate tightly with behavioral adaptations, such as reducing food-search behaviors post-feeding, which directly aligns energy intake with metabolic needs [34]. The behavioral component is particularly intriguing, as it reflects an evolutionary strategy linking metabolic feedback to appetite control—an aspect often absent in human insulin signaling. This unique function underscores the potential for developing therapies targeting both metabolic and behavioral aspects of diabetes, providing a more holistic approach to treatment. The ability of ILPs to dynamically respond under fluctuating dietary conditions further suggests their value as models for synthetic analogs designed to enhance metabolic flexibility in humans, particularly for those with insulin resistance. Moreover, unlike human insulin, ILPs show variability in their expression depending on factors such as dietary composition and energy demand. This capacity for environmental adaptation offers insights into personalized medicine applications, where therapies can be tailored to an individual's metabolic profile. Investigating the structural differences and functional efficiencies of ILPs in comparison to human insulin could lead to the design of more robust and adaptable insulin analogs with greater efficacy under varying conditions [82].

Adipokinetic hormone (AKH) in insects offers another fascinating parallel to human endocrine systems, functioning in a manner similar to glucagon by promoting energy mobilization during metabolic demand. AKH supports the release of trehalose and lipid stores from the fat body, ensuring precise energy balance and minimizing metabolic instability [49]. This glucagon-like functionality highlights AKH's potential therapeutic applicability in regulating glucose and lipid metabolism for humans. Genetic studies in *Drosophila* have demonstrated the consequences of AKH dysregulation, with null mutations in AKH or its receptor leading to excessive fat accumulation and overexpression resulting in depleted fat reserves [70]. These findings emphasize the centrality of AKH in metabolic equilibrium and suggest its utility as a target for therapies directed at both obesity and diabetes. The precision of AKH-driven enzymatic activation, facilitating the targeted release of energy reserves, offers a model for creating synthetic hormones to optimize metabolic regulation in diabetic individuals. Furthermore, AKH's dual role in reducing oxidative stress through the activation of antioxidant enzymes, such as catalase and glutathione-S-transferase, underscores its potential for treating diabetes-related complications, such as oxidative damage [70]. This dual functionality makes AKH particularly intriguing, as it addresses both glucose metabolism and oxidative stress, two major contributors to diabetes pathology. However, the systemic complexity of human endocrine systems necessitates thorough evaluation of how AKH-like mechanisms could be integrated without disrupting existing hormonal interactions [49]. The receptor specificity and upstream signaling pathways of AKH in insects provide a unique opportunity for bioengineering approaches, mimicking its metabolic efficiency in modulating glucose and lipid availability in humans.

The insulin signaling mechanisms observed in certain ant species, particularly the dual-pathway system employed by ants like *Harpegnathos saltator*, further highlight the evolutionary adaptability of insect metabolic systems. Unlike humans, who predominantly rely on the PI3 K/Akt pathway for insulin-mediated glucose regulation, ants utilize a dual-pathway model where brain-derived ILPs selectively activate the MAPK pathway within the fat body and ovaries, bypassing the PI3 K/Akt pathway [34]. This alternative pathway provides metabolic flexibility, allowing ants to optimize glucose and lipid handling under different dietary and environmental conditions. In contrast, disruptions in the PI3 K/Akt pathway in humans are closely linked to the development of insulin resistance and type 2 diabetes [83–85]. The selective activation of the MAPK pathway in ants offers a compelling framework for exploring alternative therapeutic targets in insulin signaling, presenting the possibility of bypassing dysfunctional pathways to improve metabolic resilience in human diabetes management. The ability of ants to fine-tune energy distribution across tissues by activating distinct pathways underscores

a sophisticated regulatory system that could inform the design of tissue-specific therapies for humans. However, leveraging such an approach demands meticulous research to ensure compatibility within the human endocrine landscape, given the intricate interplay of signaling networks in human physiology. The evolutionary pressures that have shaped these dual-pathway systems in ants provide a valuable blueprint for bioengineering alternative insulin signaling mechanisms in humans [34].

Dietary challenges in insects, such as high sucrose intake, have revealed remarkable gene expression adaptations that improve glycemic control and metabolic balance. Research on *Drosophila melanogaster* has identified the downregulation of insulin-like peptide 2 (ILP-2) and insulin receptor (InR) and the upregulation of insulin-like growth factor binding protein L2 (Imp-L2) under high-sugar conditions, showcasing an effective feedback mechanism for preventing hyperglycemia [33]. These regulatory adjustments reduce extracellular glucose uptake and mitigate the risk of metabolic overload, offering a model for adaptive insulin pathway modulation in humans. The upregulation of Imp-L2, which binds to ILPs and regulates their activity, further underscores the sophistication of this system in maintaining glucose homeostasis. Translating these findings into human therapies could involve the use of gene-editing technologies, such as CRISPR, to engineer targeted regulatory mechanisms that adjust insulin signaling in response to dietary sugars. This dynamic interplay between ILP-2, InR, and Imp-L2 highlights the potential for personalized medicine strategies that fine-tune insulin activity without the risk of over-suppression, which can be a limitation of conventional pharmacological interventions for diabetes [33]. However, the broader implications of such genetic modifications on the complex regulatory network of human metabolism demand comprehensive research to ensure safety and efficacy.

Neuropeptide F (NPF), the insect analog of neuropeptide Y in humans, plays a significant role in nutrient signaling and energy balance, further illustrating the intricate metabolic systems of insects. In *Drosophila*, genetic knockdown of NPF has been shown to result in reduced glucose and triglyceride levels, demonstrating its dual role in sugar and lipid homeostasis [72]. This regulatory capability offers insights into therapeutic targets for addressing obesity and hyperglycemia, which are central concerns in type 2 diabetes. Given NPF's role in balancing nutrient availability with metabolic storage needs, its pathways could serve as a model for interventions aimed at achieving a balanced metabolic state in humans. These findings suggest the potential for developing peptide-based drugs that target NPF-related receptors to manage appetite and glucose levels in diabetic patients. Furthermore, the ability of NPF to influence the tricarboxylic acid (TCA) cycle and maintain mitochondrial function underlines its broader significance in cellular energy metabolism. Comparative research between insect NPF and human neuropeptide Y could provide valuable insights for designing multifaceted therapies that address both glycemic and lipid management in diabetes [48].

The systemic effects of Bacillus Calmette-Guérin (BCG) vaccination on glucose metabolism further underscore the parallels between metabolic-immune interactions in insects and humans. Studies have shown that BCG vaccination enhances glucose uptake in human monocytes and the spleen, with a reported 47% increase in spleen glucose uptake following treatment [86]. This phenomenon reflects an integrated metabolic-immune system reminiscent of those observed in social insects, where energy and immune demands are closely intertwined. The insights gained from insect models highlight the potential for immune-modulating strategies to influence glucose homeostasis in humans. This opens a unique interdisciplinary research avenue, combining entomology and immunology to develop innovative diabetes therapies [82]. The ability of immune modulation to impact systemic glucose profiles suggests opportunities for designing insulin-independent therapies targeting tissue-specific glucose metabolism. However, the long-term viability and safety of such approaches in human systems require careful evaluation to avoid unintended consequences.

The hormonal and genetic similarities between insect and human metabolic systems provide a wealth of opportunities for advancing diabetes research and treatment. The dynamic adaptability and precision of insect mechanisms, such as those involving ILPs, AKH, and NPF, offer compelling insights into metabolic regulation under various environmental and dietary conditions. Translating these findings into human applications will require interdisciplinary collaboration and meticulous research to address the inherent complexities and ensure safe and effective integration into human therapies.

Enzymatic innovations for metabolic flexibility

Enzymatic innovations in the metabolism of bees and ants provide valuable insights into maintaining glucose homeostasis and offer a promising foundation for exploring alternative approaches to managing diabetes in humans. One pivotal enzyme, trehalose-6-phosphate synthase (TPS), catalyzes the synthesis of trehalose, a disaccharide that serves as a stable and efficient energy storage molecule in insects. Unlike humans, who rely heavily on glycogen as the primary energy reserve, insects employ trehalose to maintain metabolic equilibrium under sugar-rich conditions. The unique properties of

trehalose, including its resistance to enzymatic degradation and oxidative damage, make it an ideal candidate for facilitating energy storage and release with greater precision than glycogen [87]. By mimicking the enzymatic pathways associated with trehalose in humans, it may be possible to mitigate glucose fluctuations, a challenge central to diabetes management. The stability of trehalose as a glucose reservoir highlights not only its potential to reduce postprandial hyperglycemia in humans but also its overarching role as a safeguard against metabolic imbalances. However, implementing this approach in human systems would require extensive bioengineering studies to address compatibility issues, such as enzyme functionality and immune responses, particularly given the inherently glucose-centric nature of human metabolism [47, 49].

The complementary enzyme trehalase, which hydrolyzes trehalose into glucose, ensures the controlled release of energy in alignment with immediate metabolic demands in bees and ants. The precision with which trehalase activity is regulated in these insects minimizes the risk of metabolic overload, a mechanism that could be transformative for glycemic regulation in humans. Because humans lack endogenous trehalose metabolism, they are unable to benefit from this buffering system, which can effectively prevent sharp glucose surges. If trehalase-like enzymatic systems were introduced into human metabolic pathways, they could provide a novel solution to stabilizing blood sugar levels, particularly in individuals with impaired glucose homeostasis. Additionally, the ability of bee and ant trehalase enzymes to process sugars even under conditions of dietary excess offers a blueprint for developing interventions that reduce cellular stress associated with hyperglycemia, a hallmark of diabetes complications. However, such bioengineering initiatives face significant technical and regulatory challenges, including ensuring the safe integration of trehalase activity into human physiology without disrupting the pre-existing metabolic milieu [40, 47].

In addition to specialized enzymes, the sugar transport mechanisms of insects, particularly the glucose transporter (GLUT) system, reveal remarkable adaptability in maintaining cellular glucose homeostasis. GLUT homologs in bees and ants demonstrate enhanced regulatory precision, allowing for the efficient uptake and storage of sugars in response to metabolic demands. This contrasts with the human GLUT system, which is often compromised in insulin-resistant states, leading to imbalances in glucose distribution and energy availability. By studying the optimization of insect sugar transporters, researchers could identify potential avenues for refining glucose uptake and utilization in humans. For instance, adaptive glucose allocation mechanisms observed in ants highlight the possibility of designing therapeutic strategies aimed at improving tissue-specific glucose uptake in insulin-resistant organs, such as skeletal muscle and adipose tissue. Furthermore, the ability of bee transporters to rapidly respond to energetic demands under varying conditions could inform the development of interventions that enhance metabolic flexibility in humans. However, the evolutionary differences in sugar transport systems between insects and humans necessitate careful evaluation of how such strategies could be implemented to complement or enhance human GLUT function without introducing unintended metabolic disruptions [48, 49].

The metabolic resilience of insects can also be observed in the context of prolonged high-glucose diets. Studies on diabetic silkworm models have shown that these insects can maintain functionality and even regulate glycogen storage effectively under hyperglycemic conditions [55]. Unlike humans, who frequently experience reduced glycogen synthesis efficiency due to chronic hyperglycemia, silkworms demonstrate the capacity to buffer the deleterious effects of excessive glucose intake through enzymatic flexibility. This resilience underscores the need to study insect enzymatic systems further, with the aim of identifying mechanisms that could bolster glycogen production and stabilization in humans. If similar pathways could be bioengineered into human metabolic systems, they might alleviate key complications of diabetes, such as diminished glycogen storage capacity and glucose-induced cellular stress. However, translating such pathways into therapeutic applications would also require addressing concerns regarding long-term safety, enzyme activity modulation, and the broader implications for systemic glucose metabolism in humans [55].

The gene expression adaptations observed in insects during dietary stress further illustrate the potential for enzymatic interventions to enhance human glucose regulation. For instance, *Drosophila melanogaster* adapts to high-sugar diets by downregulating genes such as insulin-like peptide 2 (ILP-2) and insulin receptor (InR) while upregulating insulin-like growth factor binding protein L2 (Imp-L2) [33]. These modifications allow insects to prevent overstimulation of insulin pathways and maintain metabolic equilibrium. Introducing similar regulatory patterns into human systems via gene-editing technologies, such as CRISPR, could offer a tailored approach to managing hyperglycemia and preventing insulin resistance. The dynamic interplay between ILP-2, InR, and Imp-L2 highlights the potential for therapies that not only stabilize glucose levels but also provide adaptive responses to fluctuating dietary conditions. However, the complex feedback mechanisms governing human metabolism present

significant hurdles to implementing such strategies, as interventions must accommodate the systemic and multifaceted nature of human glucose regulation while minimizing the risk of unintended effects [33].

The concept of distributed robustness, a characteristic of insect metabolic networks, offers an additional layer of insights for developing human diabetes therapies. Insects achieve metabolic resilience by incorporating redundant and synergistic pathways, such as the complementary actions of TPS and trehalase. This distributed nature ensures that failures in one pathway do not lead to catastrophic metabolic outcomes, a feature that could inspire more robust therapeutic designs for humans. For instance, integrating trehalose-based enzymatic systems into human metabolism could create redundancy, providing a safety net to stabilize glucose levels during dietary changes or metabolic stress. Similarly, combinatorial therapies that mimic the synergistic effects of insect enzymes may offer an innovative approach to addressing both glucose regulation and energy storage challenges simultaneously. However, the human metabolic system's higher complexity and interconnectivity require a nuanced understanding of how such distributed strategies could be implemented without introducing new vulnerabilities or interactions that offset their intended benefits [88].

The broad spectrum of enzymatic innovations evident in bee and ant metabolism underscores their immense potential to shape novel approaches for managing diabetes. From the stabilization offered by trehalose metabolism to the dynamic regulatory capacity of sugar transport systems, these insights pave the way for reimagining human therapies. Future research should focus on bridging the gaps between insect and human metabolism while addressing the technical, biological, and safety challenges inherent in such translational endeavors.

Bioengineering and precision medicine opportunities

The exploration of bioengineering and precision medicine opportunities rooted in the metabolism of bees, ants, and other insects offers a promising frontier in addressing diabetes management challenges (Fig. 6). Insights from the structural and functional similarities between insulin-like peptides (ILPs) in insects and human insulin provide a compelling foundation for the development of novel therapeutic analogs. ILPs regulate sugar metabolism by promoting glucose uptake and energy storage, resembling the primary actions of human

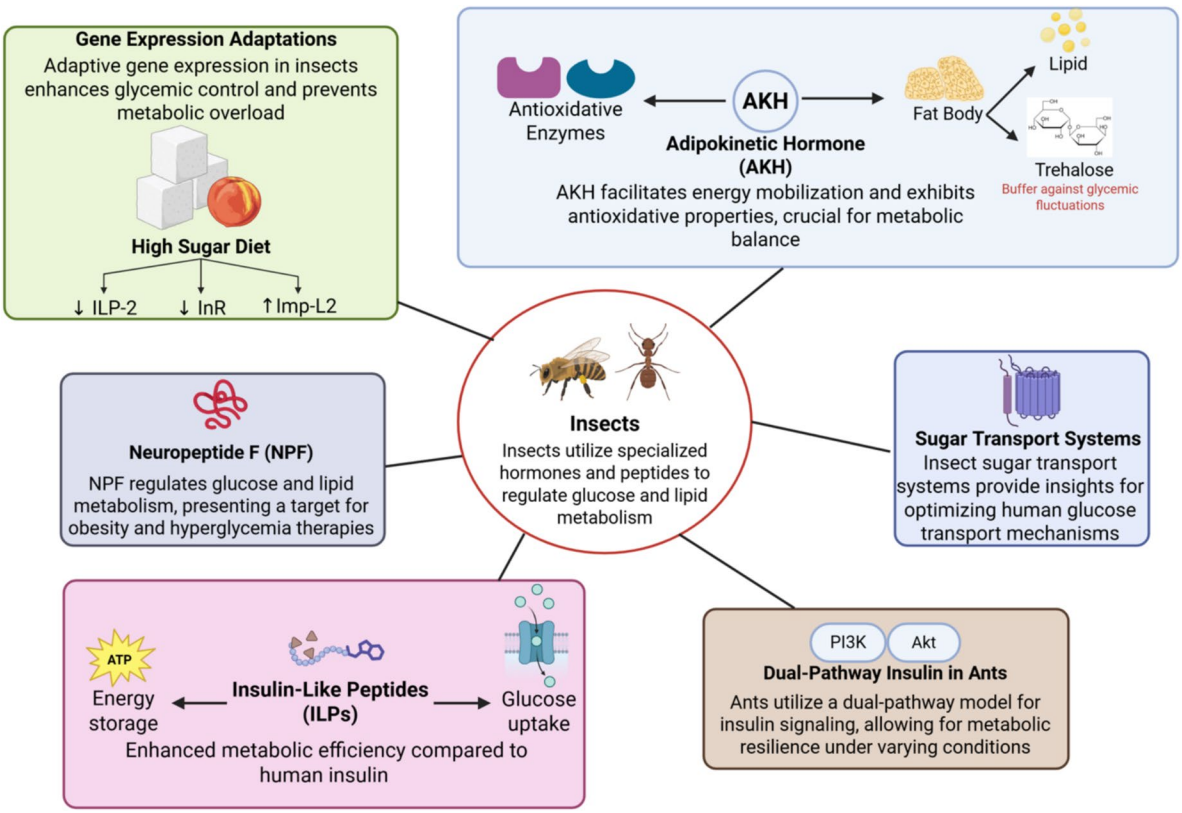

Fig. 6 Diabetes Management Inspired by Insect Metabolism

insulin. However, ILPs demonstrate enhanced metabolic efficiency and flexibility, as seen in their ability to adjust dynamically to dietary changes and environmental demands. Notably, ILPs integrate metabolic regulation with behavioral energy intake adjustments, such as reducing food-search behaviors post-feeding [49]. This dual functionality offers a model for designing therapies that address both biological and behavioral aspects of diabetes management. While ILPs hold potential for developing insulin analogs capable of overcoming issues like insulin resistance, further investigation is required to assess the long-term efficacy and safety of such peptides in humans and ensure precise targeting without disrupting existing endocrine processes [34, 82].

Adipokinetic hormone (AKH), an insect hormone analogous to human glucagon, provides a powerful example of efficient energy mobilization. AKH facilitates the release of trehalose and lipid stores from the fat body, maintaining metabolic balance during periods of increased energy demand. Genetic studies in *Drosophila* have revealed that mutations affecting AKH or its receptor (AKHR) result in severe metabolic imbalances, such as excessive fat accumulation or lipid depletion, emphasizing the hormone's regulatory importance. Additionally, AKH exhibits antioxidative properties by activating enzymes like catalase and glutathione-S-transferase, suggesting its broader therapeutic applicability in managing oxidative stress, a common diabetes complication. Integrating AKH-like mechanisms into human therapies could provide dual benefits in regulating glucose and lipid metabolism while mitigating oxidative damage. However, human endocrine complexity and the interplay of glucagon with other hormones necessitate extensive research to adapt AKH-driven mechanisms safely into human systems without unintended metabolic disturbances [49, 70].

In certain ant species, the dual-pathway insulin signaling system offers a unique model of metabolic flexibility and resilience. Unlike humans, who predominantly rely on the PI3 K/Akt pathway for insulin-regulated glucose metabolism, ants employ an additional MAPK pathway activated by brain-derived ILPs. This dual-pathway model allows ants to adapt energy distribution across tissues efficiently under varying dietary or environmental conditions. By comparison, disruptions in the human PI3 K/Akt pathway are closely associated with insulin resistance and type 2 diabetes. The ability to bypass or complement dysfunctional insulin signaling through an alternative pathway, as seen in ants, presents an intriguing avenue for therapeutic intervention. However, the intricate complexity of human insulin systems poses significant challenges for translating these mechanisms, as interventions may require tissue-specific targeting to avoid broader systemic imbalances. Rigorous studies are needed to fully understand how dual-pathway signaling models can inform the design of therapies that enhance metabolic resilience in humans [34, 49].

Gene expression adaptations in insects, particularly under high-sugar dietary conditions, illuminate effective strategies for managing hyperglycemia. Research on *Drosophila melanogaster* has shown that downregulation of insulin-like peptide 2 (ILP-2) and insulin receptor (InR) expression, coupled with upregulation of insulin-like growth factor binding protein L2 (Imp-L2), enhances glycemic control and prevents metabolic overload. This regulatory mechanism ensures a balance between insulin activity and glucose uptake, reducing the risks associated with prolonged hyperglycemia. Translating such adaptive genetic pathways into human therapies could involve precision medicine approaches, including CRISPR gene-editing technologies, to modulate insulin signaling dynamically. However, the multifaceted feedback systems involved in human glucose regulation introduce challenges for implementing such interventions, particularly in achieving the necessary specificity and avoiding adverse effects on systemic metabolism [33].

The role of neuropeptides, such as neuropeptide F (NPF) in insects, further underscores the intricate coupling of nutrient signaling and energy balance. NPF, which is analogous to neuropeptide Y in humans, regulates glucose and lipid metabolism in *Drosophila*. Experiments have shown that genetic knockdowns of NPF reduce glucose and triglyceride levels, demonstrating its influence over both sugar metabolism and fat storage. The potential to target NPF-like pathways in humans represents an innovative approach to addressing obesity and hyperglycemia, two major drivers of type 2 diabetes. Additionally, NPF's influence on mitochondrial function and the tricarboxylic acid (TCA) cycle highlights its broader significance in cellular energy metabolism. However, comparative studies are necessary to identify the parallels and divergences between insect NPF and human neuropeptide Y, as these differences could shape the development of effective and safe therapeutic strategies [48, 72].

The systemic effects of Bacillus Calmette-Guérin (BCG) vaccination in type 1 diabetes patients provide an intriguing parallel to metabolic-immune interactions commonly observed in social insects. In humans, BCG vaccination has been shown to enhance glucose uptake in monocytes and the spleen, suggesting a potential link between immune-modulating strategies and glucose homeostasis. This observation resonates with the tightly integrated metabolic-immune systems of social insects, where energy demands are often aligned with immune responses. While the relevance of these

metabolic-immune interactions to diabetes management is still being explored, the findings highlight the potential of combining immune-modulating therapies with metabolic interventions inspired by insect physiologies [86].

The enzymatic pathway involving trehalose-6-phosphate synthase (TPS) in insects offers a promising model for metabolic flexibility in humans. TPS catalyzes the production of trehalose, a stable disaccharide that serves as a primary circulating sugar in insects, providing a buffer against glycemic fluctuations. By incorporating trehalose-based pathways into human systems, it may be possible to reduce postprandial hyperglycemia and enhance metabolic stability. However, the glucose-centric nature of human metabolism presents significant barriers to introducing trehalose mechanisms, including potential immune responses and compatibility issues. Further research is required to assess the feasibility of incorporating TPS into human therapies while addressing these technical and safety considerations [40, 49].

Trehalase, the enzyme responsible for hydrolyzing trehalose into glucose, plays a critical role in the controlled release of energy in insects. Its precise regulation minimizes metabolic overload, a mechanism that holds significant potential for human diabetes therapy. Introducing trehalase-like enzymatic systems into human physiology could provide a novel solution for stabilizing blood sugar levels, particularly in diabetic patients prone to glucose spikes. However, the absence of endogenous trehalose metabolism in humans raises questions about how such an intervention could be safely integrated without interfering with existing metabolic pathways. Addressing these challenges will require innovative bioengineering approaches and extensive preclinical studies [40, 47].

The study of sugar transport systems, particularly the glucose transporter (GLUT) analogs in bees and ants, underscores the potential for optimizing human glucose transport mechanisms. Insects exhibit advanced regulatory features in their sugar transport systems, ensuring efficient glucose uptake and energy distribution even under dietary stress. These attributes provide a blueprint for enhancing human GLUT function, especially in tissues affected by insulin resistance. However, the evolutionary divergence between insect and human transport systems demands careful evaluation of how these strategies might be adapted without unintended consequences for glucose homeostasis [48, 49].

Research on diabetic silkworm models has revealed insights into the enzymatic resilience of insect metabolism under high-glucose conditions. Unlike humans, who often experience reduced glycogen synthesis efficiency under hyperglycemia, silkworms effectively stabilize glycogen storage through flexible enzymatic pathways. Mimicking these pathways in human therapies could mitigate some of the complications associated with chronic hyperglycemia, including impaired glycogen storage. However, translating these mechanisms into clinical applications will necessitate addressing compatibility issues and ensuring long-term safety in human metabolic systems [55].

Gene expression modifications in insects, such as the upregulation of Imp-L2 and the downregulation of ILP-2 and InR in response to high-sugar diets, highlight adaptive strategies for maintaining glucose homeostasis. Introducing similar regulatory mechanisms into human systems could provide a tailored approach to managing hyperglycemia and mitigating insulin resistance. Precision medicine techniques, such as CRISPR, offer promising tools for realizing this potential, but the systemic complexity of human metabolism necessitates extensive validation and safety assessments for such interventions [33].

The distributed robustness evident in insect metabolic systems offers an innovative framework for designing resilient human therapies. Insects achieve metabolic stability through redundant and synergistic pathways, such as the complementary roles of TPS and trehalase. Introducing similar redundancy into human metabolic pathways could enhance the robustness of glycemic control and reduce the risks associated with single-point failures in metabolism. However, the high complexity of human metabolic networks requires careful integration of such strategies to avoid unintended interactions that might compromise overall stability [88].

Extending these opportunities further, edible insects such as bees and ants, which are increasingly recognized for their nutritious components, provide additional avenues for therapeutic development. Bee pollen exemplifies this potential, as it is composed of bioactive compounds, including proteins, amino acids, lipids, carbohydrates, minerals, vitamins, and polyphenols. These compounds collectively enhance various bodily functions and offer protection against disease. Moreover, bee pollen has been historically recognized as a functional food with significant therapeutic properties, which can be leveraged for improving glycemic control and overall metabolic health. Studies indicate that bee pollen may have applications in regulating glucose levels and promoting metabolic efficiency, making it a valuable candidate for adjunct therapies in diabetes management [44, 89].

Bee pollen and its derivatives also illustrate a bridge between traditional medicine and modern therapeutic practices, particularly in regions such as Tanzania, where traditional medicines are a primary healthcare source. The integration of insect-derived compounds into culturally relevant treatment strategies could bolster their acceptance and effectiveness. With millions of

individuals worldwide including insects as part of their diet, edible insects represent an underutilized yet promising resource for combating diabetes and its related complications. However, sustainable harvesting and ethical considerations for utilizing these resources must also be addressed to ensure minimal environmental and social impact [44, 89].

The diverse insights derived from the metabolic systems of social insects, spanning hormonal, genetic, and enzymatic innovations, highlight the immense potential for transforming diabetes therapy. These models provide a foundation for bioengineering and precision medicine approaches, offering new perspectives to address the challenges of glycemic regulation with greater efficacy and safety.

Current challenges in translational diabetes research

Translating the metabolic adaptations of insects such as bees and ants into human diabetes therapies presents significant biological challenges (Fig. 7). A major obstacle is the absence of native trehalose metabolism in humans, a metabolic centerpiece for energy regulation in these insects. Insects utilize trehalose along with enzymes like trehalose-6-phosphate synthase (TPS) and trehalase to regulate blood sugar and store energy efficiently, but humans rely predominantly on glycogen. The absence of a comparable enzymatic system in humans raises profound questions about how trehalose-based pathways could be safely incorporated into human physiology. Synthetic pathways or trehalose analogs might be designed to emulate this system, but their structural and functional compatibility with existing glucose-centric human metabolism would need to be addressed comprehensively. Furthermore, the introduction of such pathways would have to avoid immune responses and ensure that glucose regulation dynamics are not disrupted. Long-term impacts on enzymatic stability, cellular energy balance, and broader systemic glucose dynamics could also pose risks. These biological differences underscore the evolutionary divergence between humans and insects and the necessity of understanding both the similarities and limits in translating these mechanisms for therapeutic applications [40, 44].

The technical barriers to adapting hormonal mechanisms from insects to humans, such as insulin-like peptides (ILPs) and adipokinetic hormone (AKH), are significant. Although ILPs share structural and functional similarities with human insulin and regulate sugar metabolism effectively in insects, their biochemical environment and receptor interactions differ substantially. ILPs perform in contexts with receptors and signaling pathways that do not exist in humans, such as tissues uniquely adapted to insect physiology. Similarly, AKH performs glucagon-like functions, mobilizing energy reserves in insects, but interacts with specialized receptors absent in human systems. Adapting these mechanisms would likely require the development of synthetic analogs or receptor mimetics tailored to human biology. For example, leveraging AKH's role in glucose and

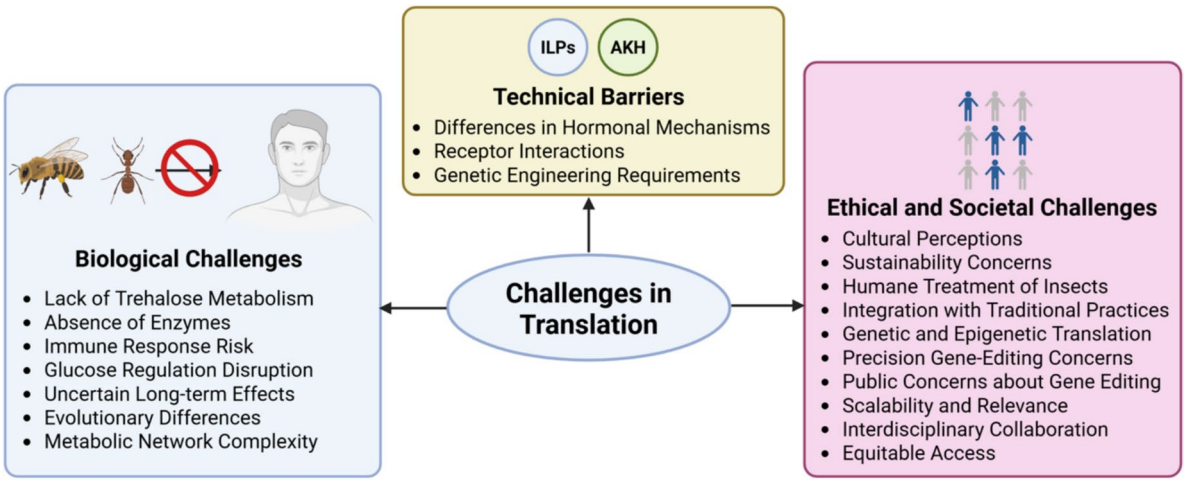

Fig. 7 Challenges in Translating Insect Metabolic Strategies into Human Therapies. This figure summarizes key challenges associated with translating insect metabolic mechanisms into therapeutic strategies for human diabetes management. Challenges are categorized into three major domains: (1) Biological challenges, including the absence of trehalose metabolism and certain enzymatic systems in humans; (2) Technical barriers, such as hormonal mechanism differences, receptor interactions, and genetic engineering requirements; and (3) Ethical and societal challenges, addressing cultural perceptions, sustainability, humane treatment of insects, and ethical concerns surrounding gene editing. Overall, the figure emphasizes the need for multidisciplinary collaboration to responsibly and effectively translate insect-based therapies into clinical practice

lipid metabolism and its antioxidative capabilities could theoretically ameliorate both hyperglycemia and oxidative stress in diabetes patients. However, designing such systems would demand extensive research to ensure that these analogs interact effectively and safely with human signaling networks. In addition, the dual-pathway insulin signaling observed in ants, which involves both the PI3 K/Akt and the alternative MAPK pathways, offers potential models for metabolic resilience that could bypass the faulty PI3 K/Akt pathway in insulin-resistant humans. However, replicating these pathways in human systems would necessitate intricate genetic engineering and biochemical interventions to achieve tissue-specific targeting, raising concerns about inadvertently disrupting other physiological processes [33, 34, 49].

Regulatory hurdles add another layer of complexity to translating insect-derived insights into diabetes therapies. For instance, compounds such as glycosaminoglycan (GbG) from field crickets have demonstrated antihyperglycemic effects in preclinical studies, but there is a long road to achieving regulatory approval for human use. Such approval processes demand comprehensive validation through rigorous preclinical trials and multiple phases of clinical testing to ensure safety and efficacy. Variability in genetic and lifestyle factors among humans adds an additional layer of complexity in demonstrating consistent therapeutic outcomes. These variations can challenge the uniformity required by regulatory frameworks. Another issue lies in the classification of insect-derived products, particularly whether they are categorized as functional foods or pharmaceuticals. This distinction significantly influences the evidentiary standards required for approval, with pharmaceuticals often facing more stringent regulatory pathways. The financial and temporal burden of meeting regulatory requirements presents a further impediment, particularly for small-scale researchers or startups. Collaborative efforts among industry stakeholders, researchers, and regulatory bodies could help streamline these processes and foster a more supportive environment for innovation in this domain [40, 90].

Ethical and societal challenges are also critical considerations when scaling the use of insect-derived products for diabetes treatment. Cultural perceptions of insects vary widely across regions, with strong resistance in certain societies against using insect-based therapies or food products. While over 2 billion people globally already incorporate insects into their diets, introducing insect-derived medications or supplements may require robust educational campaigns and public health messaging to overcome stigma and promote acceptance [91, 92]. Sustainability is another pressing concern, particularly in relation to large-scale insect farming. Producing sufficient quantities of insects or their derivatives could strain ecosystems, potentially leading to the depletion of wild insect populations or disruptions in biodiversity [93]. This is particularly critical for bees and ants, which are integral to pollination and ecosystem stability. Industrial-scale farming must carefully balance pharmaceutical demands with environmental conservation to avoid unintended ecological consequences. Ethical guidelines, including measures to ensure the humane treatment of insects, should also be established to define the scope of insect farming practices and maintain ecological balance. Additionally, traditional medical practices, especially in regions like Tanzania where up to 80% of health care relies on natural or cultural medicines, could benefit from a well-managed integration of insect-derived compounds. As these products are incorporated into therapeutic approaches, aligning them with culturally accepted practices could enhance acceptance and accessibility [44].

Another significant barrier involves translating the genetic and epigenetic insights gained from insect models, such as *Drosophila melanogaster*, into human-relevant contexts. Genes like ILP-2, insulin receptor (InR), and insulin-like growth factor binding protein L2 (ImpL2) regulate sugar metabolism in insects and represent potential targets for addressing diabetes in humans. However, implementing these genes or modifying analogous pathways in humans poses substantial challenges because of fundamental differences in genetic architecture and regulatory networks. Precision gene-editing technologies such as CRISPR offer tools for such interventions, but ensuring specificity and avoiding off-target effects remains a concern. The broader metabolic implications of altering such critical regulatory genes would need to be carefully studied to prevent unanticipated physiological consequences. Additionally, translating epigenetic mechanisms from insects to humans is constrained by the complexity and variability of human epigenetic landscapes. For instance, regulatory systems adapted to the fat body in bees would require substantial contextual modification to align with human adipose tissue function. Ensuring the safety and ethical acceptability of gene-editing technologies further complicates these efforts, with public concerns about misuse or unintended ecological impacts necessitating clear regulatory oversight [33, 90].

The integration of insect-derived metabolic mechanisms into precision medicine for diabetes treatment also faces unique challenges related to scalability and relevance. The metabolic systems of bees and ants are finely tuned to their ecological roles and high-sugar diets, which makes their direct translation into human systems inherently complex. While these insects metabolize

energy efficiently to support colony-level demands, scaling these mechanisms to meet the metabolic needs of individual humans requires substantial modifications. Current research remains limited in scope, with many findings confined to insect models without adequate testing in mammalian systems. Bridging this gap will require interdisciplinary collaborations that integrate insights from entomology, pharmacology, and biomedicine. Additionally, the development of scalable biotechnologies, such as engineered probiotics or synthetic enzymatic pathways, is essential to implement insect-inspired therapies in a cost-effective and accessible manner. Human dietary and metabolic diversity further complicates the application of these therapies, necessitating treatments that are adaptable across various populations and individualized contexts. Collaborative frameworks that incorporate ecosystem sciences, public health perspectives, and ethical considerations will be crucial in ensuring both the equitable and responsible application of these innovations [44, 94].

Expanding insect-derived metabolic insights into diabetes research and treatment involves substantial biological, technical, regulatory, ethical, and practical challenges. While these translational barriers are significant, they also highlight opportunities for progress through interdisciplinary collaboration, technological innovation, and a commitment to sustainable and ethical practices.

Future prospects and research directions

The integration of multi-omics platforms in metabolic research offers a profound opportunity to deepen our understanding of how bees and ants maintain efficient glucose homeostasis. Combining genomics, transcriptomics, proteomics, and metabolomics enables a holistic approach to studying these intricate metabolic systems. Genomic studies, for example, can reveal genetic variations that underpin unique traits such as the dual-pathway insulin signaling system observed in certain ants. This mechanism, which allows metabolic flexibility by bypassing traditional human pathways, such as PI3 K/Akt signaling, has the potential to inspire innovative interventions for human diabetes therapies. Simultaneously, transcriptomic analyses can elucidate gene expression changes triggered by environmental or dietary stresses, offering actionable insights into adaptive responses [95]. Proteomics contributes by identifying and characterizing key proteins, such as trehalose-6-phosphate synthase (TPS) and trehalase, which regulate trehalose metabolism in insects. Their roles in energy storage and release, entirely absent in human systems, present an exciting avenue for therapeutic development. Additionally, metabolomic studies provide a critical layer of understanding by tracking the production and utilization of metabolites, such as trehalose, glycogen, and glucose, under variable dietary conditions. Insights from these studies can illuminate mechanisms that confer metabolic resilience to bees and ants, enabling the design of interventions to replicate these traits in humans. However, integrating these datasets into actionable interventions is not without challenges. Differences in metabolic networks across species and the complexity of aligning insect-derived mechanisms with human biology must be carefully navigated. Furthermore, cross-species models that leverage multi-omics data will require extensive validation to ensure both efficacy and safety in human systems.

The development of bioengineered probiotics holds significant promise as an innovative approach to diabetes management. These probiotics, inspired by compounds like glycosaminoglycan (GbG) from field crickets, have already demonstrated antihyperglycemic and antioxidant properties in preclinical studies involving diabetic mice. GbG has shown the ability to lower blood sugar levels, inhibit markers like LDL-cholesterol and alkaline phosphatase, and mitigate protein oxidation while enhancing antioxidant enzyme activities. This dual role in addressing oxidative stress and hyperglycemia makes it a promising compound for further exploration [40]. Building on this foundation, probiotics engineered to express enzymes such as trehalose-6-phosphate synthase (TPS) could enable the localized production of trehalose in the human gut. This capability could serve to stabilize blood glucose levels, particularly under diets high in sugars, while mitigating glycemic spikes associated with diabetes. Furthermore, by integrating genes responsible for antioxidant production, these probiotics could address oxidative stress—a major contributor to diabetes-related complications such as neuropathy and nephropathy. Additionally, the ability of such probiotics to interact with gut microbiota could enhance nutrient absorption and improve overall glycemic control, creating a multipronged therapeutic effect. While these opportunities are encouraging, the scalability and long-term safety of engineered probiotics remain significant concerns. Interactions with existing gut microbiome communities must be rigorously evaluated to avoid adverse effects such as dysbiosis or unintended immune responses. The stability of probiotic functionality over extended periods and the ethical considerations of genetically modifying live organisms for therapeutic use further underscore the need for robust research and regulatory oversight.

The exploration of neuropeptide-based therapies, inspired by the functional analogies between insect neuropeptide F (NPF) and human neuropeptide Y, introduces a novel dimension to metabolic and appetite

regulation research. NPF has been shown, in genetic knockdown studies using *Drosophila melanogaster*, to influence both glucose and triglyceride levels [72]. This dual regulatory capacity highlights its potential as a therapeutic target for addressing the dysregulated appetite and high blood glucose levels characteristic of diabetes. Modulation of NPF signaling could reduce overeating behaviors and improve glycemic control, as previously observed in insect models [96]. Further studies have shown the broader applicability of insect peptides in addressing human diseases, noting their structural and functional homologies to mammalian peptide hormones, including roles in immune modulation and metabolic regulation [48]. Furthermore, the role of neuropeptides in stress response regulation and the mitigation of oxidative stress provides an additional therapeutic angle, given the significant role of oxidative damage in diabetes complications [97]. Comparative studies of neuropeptide systems in bees and ants, particularly their energy allocation strategies, may yield further insights into designing effective neuropeptide-based treatments for human metabolic disorders. However, the translation of these findings into human therapies faces multiple challenges. Neuropeptides often have widespread physiological roles, so precisely targeting metabolic pathways without inadvertently affecting non-metabolic systems is crucial. Advanced drug delivery mechanisms will be essential to ensure efficacy and minimize off-target effects.

The use of self-regulation dietary approaches to improve glycemic control represents a promising behavioral intervention in diabetes management. Behavioral frameworks based on self-regulation models have demonstrated significant efficacy, as evidenced in a recent study where type II diabetic patients experienced a marked improvement in blood sugar control, reducing levels from 162.3 to 128.9 mg/dl. This program also resulted in enhanced dietary and exercise behaviors, knowledge acquisition, and overall self-efficacy for glycemic management [98]. Insights from the dietary regulation strategies of bees and ants could enhance these approaches. Social insects demonstrate remarkable flexibility in sugar intake management, dynamically adjusting their diets to align with colony needs without experiencing metabolic dysfunction. Such strategies could inform human self-regulation programs, enabling individuals to adapt their dietary behaviors in real time based on metabolic feedback. Combining these behavioral interventions with educational initiatives could further empower patients to actively participate in their diabetes management, fostering long-term adherence to therapeutic regimens. Advances in technology, such as mobile applications and wearable devices, could support self-regulation by providing real-time data on blood glucose levels and dietary intake, mirroring the feedback systems inherent in social insect energy regulation. Nevertheless, sustainable implementation of these approaches requires consideration of cultural, social, and economic factors that may influence patient compliance and accessibility.

The application of gene-editing technologies, such as CRISPR, to replicate metabolic adaptations observed in insects presents a cutting-edge prospect for diabetes therapy. Downregulating genes like insulin-like peptide 2 (ILP-2) and insulin receptor (InR) while upregulating insulin-like growth factor binding protein L2 (Imp-L2), as demonstrated in *Drosophila melanogaster*, could offer a novel pathway for enhancing glucose homeostasis and insulin sensitivity in humans [33]. Additionally, the dual-pathway insulin signaling observed in ants, which incorporates alternative mechanisms such as MAPK activation, provides a compelling blueprint for bypassing dysfunctional pathways in insulin-resistant patients. These interventions could potentially alleviate key bottlenecks associated with traditional insulin signaling pathways, offering greater metabolic flexibility. Furthermore, gene-editing strategies could target oxidative stress resilience mechanisms, such as those linked to adipokinetic hormone (AKH), to address complications stemming from chronic hyperglycemia. However, the implementation of such strategies must be approached with caution, as the potential for off-target effects poses significant risks. The broader ethical and societal implications of gene editing for therapeutic purposes also demand robust regulatory frameworks and public engagement to ensure acceptance and responsible utilization.

Sustainable and ethical frameworks are essential for the large-scale integration of insect-derived therapies into diabetes management. The production of compounds such as glycosaminoglycan (GbG) and components of royal jelly requires sustainable farming practices that prioritize the conservation of biodiversity and pollination ecosystems. Synthetic alternatives or biotechnological innovations could alleviate environmental pressures and reduce reliance on insect populations. Ethical considerations, including the humane treatment of insects during farming, must also be addressed to align production practices with international welfare standards. Equitable access to these therapies is critical, particularly in low-income regions heavily dependent on traditional medicine. Efforts to make such treatments affordable and accessible could reduce healthcare disparities and improve outcomes for underserved populations. Educational campaigns to promote the benefits and safety of insect-derived products may help overcome societal resistance, particularly in regions unfamiliar or uncomfortable with the concept of using insects in medicine. Finally, establishing international regulatory standards

will be crucial to ensure the safety, efficacy, and sustainability of these therapies while facilitating their integration into existing healthcare systems.

The combination of multi-omics research, bioengineering innovations, and behavioral strategies demonstrates immense potential for advancing diabetes management. However, the challenges of translating these approaches into human applications underline the need for continued interdisciplinary research and ethical reflection to maximize their impact.

Ethical considerations and sustainability

The societal acceptance of insect-derived therapies presents a complex and multifaceted challenge, heavily influenced by regional and cultural differences in the perception of insects. While over two billion people worldwide include insects in their diet, such practices are highly variable and often stigmatized in Western cultures. Countries like Tanzania, where traditional medicine accounts for up to 80% of healthcare in rural areas, may be more receptive to incorporating insect-derived compounds for diabetes treatment due to alignment with existing health practices [44]. Addressing resistance in regions unfamiliar or uncomfortable with the concept necessitates educational campaigns that emphasize the scientific legitimacy and health benefits of such therapies. For example, presenting evidence of glycosaminoglycans' antihyperglycemic effects—such as reducing oxidative stress and blood glucose levels—can help build societal trust. These efforts need to be tailored to specific cultural narratives to ensure widespread acceptance.

Public educational initiatives play a key role in fostering societal trust towards insect-based medical solutions. By communicating the health benefits of insect-derived therapies in clear and accessible terms, public concerns can be mitigated. Highlighting the low ecological footprint of insect farming compared to traditional livestock and their potential to address global health crises could counteract entrenched cultural biases [44]. Scientific advocacy might focus on specific health outcomes, such as the reduction in blood sugar levels observed with glycosaminoglycans, to bridge the gap between scientific evidence and public understanding. The use of relatable, evidence-based messaging that ties these therapies to improved healthcare outcomes will be critical to building widespread acceptance.

Global case studies where insect-based solutions have been scaled for medicinal or nutritional uses offer valuable templates for broader application. In regions such as Southeast Asia and Sub-Saharan Africa, insects are already widely used as protein supplements in local diets, showcasing their adaptability and public acceptance [99]. This existing infrastructure could be leveraged to facilitate the introduction of bioactive compounds, such as insulin-like peptides, into diabetes therapies. These examples underscore the importance of context-specific innovation. For instance, successful models of scaling insect farming for nutritional purposes could provide insights into how to develop similar frameworks for pharmaceutical applications, ensuring both sustainability and accessibility [44].

Sustainability challenges of large-scale insect farming must be carefully navigated to balance the medical utility of insect-derived compounds with their ecological impact. While insects are often cited for their minimal resource requirements, scaling production to meet pharmaceutical demands could risk overexploitation of ecologically essential species like bees and ants [44]. Such disruptions could undermine biodiversity and agricultural productivity, given these insects' critical roles as pollinators. Sustainable farming practices, such as controlled breeding environments that minimize interference with wild populations, must be pursued to mitigate these risks. These strategies must be coupled with ongoing ecological assessments to prevent unintended environmental consequences.

The resource efficiency of insect farming highlights its potential as a sustainable alternative to traditional livestock. Insects require significantly fewer resources, including feed, water, and land, while producing minimal waste [100]. Rapid reproduction cycles further enhance their viability for scalable production. For instance, cricket farming practices already demonstrate low-impact, sustainable methods that could be adapted for cultivating species with bioactive compounds for diabetes therapies [101]. This efficiency could make insect-derived medicinal compounds both environmentally sustainable and economically viable, addressing resource constraints in global healthcare contexts [44].

Environmental preservation strategies must be integral to the development of insect-derived diabetes therapies. Synthetic replication of bioactive compounds in controlled laboratory settings offers one solution to reduce reliance on wild insect populations. For example, glycosaminoglycan synthesis could be achieved in laboratory environments, allowing for medical advancements without compromising ecological stability [40]. Such measures ensure that the scalability of these therapies does not come at the expense of biodiversity, facilitating their long-term sustainability while supporting medical innovation.

Ethical considerations in insect farming are increasingly critical as the scale of this practice expands for pharmaceutical purposes. Concerns over the humane treatment of insects and their ecological roles must be addressed to ensure both public acceptance and

ecological sustainability. Establishing humane rearing and harvesting standards is a necessary step to mitigate ethical concerns. Furthermore, ensuring that pollinators such as bees remain prioritized for their ecological contributions rather than solely their biomedical applications demonstrates a balanced approach to ethical and ecological priorities [48].

Balancing medical and ecological needs presents a significant challenge in scaling insect-derived diabetes therapies. Overharvesting bees for their metabolic compounds could risk their crucial role as pollinators, disrupting ecosystems and agricultural productivity. Captive breeding and laboratory synthesis of bioactive compounds offer viable alternatives. Developing innovative production methods that prioritize ecological preservation can maintain equilibrium between advancing medical science and sustaining natural ecosystems. This balance is crucial for ensuring the long-term viability of these therapeutic approaches [44].

Policy frameworks for ethical farming are essential to align insect farming practices with international standards for sustainability and welfare. Collaborations among governments, researchers, and NGOs can establish guidelines that prioritize ecological and ethical considerations. For example, incentivizing agricultural methods that minimize environmental disruption while facilitating the production of bioactive compounds for diabetes management can create a more sustainable model. These policies also encourage cross-sector collaboration, streamlining the integration of insect-derived solutions into global healthcare [102].

Regulatory barriers pose significant obstacles to the translation of insect-derived insights into diabetes therapies. Compounds such as glycosaminoglycans, while promising, require rigorous preclinical and clinical testing to meet international safety and efficacy standards. Additionally, genetic and environmental variability among human populations adds complexity to demonstrating consistent therapeutic outcomes, complicating approval processes. Distinctions between classifying these solutions as functional foods or pharmaceuticals further dictate the regulatory pathways they must navigate. Overcoming these barriers demands strategic collaboration to streamline regulatory validation and compliance [40].

Collaboration between governments, NGOs, and researchers is vital for addressing the regulatory complexities associated with insect-derived diabetes therapies. Partnerships can accelerate the testing and implementation of these solutions by pooling resources and expertise. For instance, government-subsidized clinical trials and funding initiatives can ensure that these innovations advance despite financial or logistical constraints. Such collaborations also foster equitable access to these therapies, particularly in underserved regions, ensuring that scientific advancements translate into tangible healthcare solutions [44].

The adaptation of global regulatory standards can facilitate the international adoption of insect-based therapies. Harmonized frameworks for preclinical and clinical testing ensure that therapeutic developments meet consistent safety and efficacy benchmarks across different regions. Organizations such as the World Health Organization (WHO) play a critical role in setting these global standards. Universal guidelines can streamline approval processes, enabling faster access to effective treatments for diabetes while maintaining a robust standard of care [77].

Ethical dilemmas in prioritizing human health over environmental concerns must be mitigated through sustainable practices. While insect-derived bioactive compounds represent significant promise for diabetes management, their extraction risks depleting vital insect populations. Synthetic biology approaches, such as engineering microbes to produce these compounds, offer a solution that minimizes ecological disruption. Balancing the benefits of these therapies with their environmental impact requires innovative approaches to ensure neither human health nor biodiversity is compromised [48].

The ecological implications of bioactive compound extraction highlight the necessity of developing alternative production methods. Relying on natural extraction could deplete insect populations critical to ecosystems. Instead, sustainable farming systems or laboratory-based synthesis should be prioritized. These innovations can simultaneously advance medical science and preserve ecological integrity, ensuring the responsible use of natural resources for therapeutic purposes [44].

Equitable access to insect-derived therapies is essential for maximizing their impact, particularly in underserved regions where traditional medicine is a primary healthcare source. For rural Tanzanian communities, affordable production and distribution of therapies derived from insect compounds could bridge gaps in healthcare access. By keeping production costs low and leveraging existing traditional medicine practices, these therapies can remain culturally relevant and accessible, improving health outcomes for vulnerable populations [44].

Collaboration with NGOs and governments can enhance the equitable distribution of insect-based diabetes treatments. Subsidizing production costs or funding clinical trials increases affordability and accessibility in low-income regions. These partnerships ensure that advancements in healthcare technology benefit all populations, reducing disparities and enhancing global health equity [102].

Long-term sustainability in the supply chains for insect-derived therapies must be prioritized to maintain consistent availability of these treatments without compromising ecological integrity. Globally coordinated networks can support the responsible scaling of production, ensuring minimal environmental impact while meeting healthcare demands. A comprehensive approach that incorporates environmental preservation, cost-effectiveness, and equitable access will be critical for addressing both the challenges of diabetes management and the broader implications of global health disparities [48].

Ethical and sustainability considerations must be central to the development and implementation of insect-derived diabetes therapies. Balancing medical innovation with ecological and societal responsibilities is essential to advancing these promising solutions in a way that ensures both scientific progress and global equity.

Conclusion

Diabetes mellitus remains a major global health burden, demanding innovative and integrative treatment strategies. This paper explored how metabolic adaptations in social insects—particularly bees and ants—can inspire novel therapeutic approaches for diabetes. These insects exhibit exceptional glycemic control via trehalose metabolism, dual-pathway insulin signaling, and hormones like insulin-like peptides (ILPs) and adipokinetic hormone (AKH), offering insights into stable energy regulation and oxidative stress mitigation. Translating these mechanisms to human therapy presents opportunities in enzymatic regulation, gene editing, and engineered probiotics, although challenges such as species differences and safety concerns remain.

This interdisciplinary study bridges entomology, molecular biology, and precision medicine, emphasizing how nature-inspired models can fill current therapeutic gaps. It also supports the development of sustainable and accessible solutions, particularly for low-resource settings. However, experimental validation, ethical considerations, and scalability must guide future research. Overall, leveraging insect metabolism provides a promising framework for biomimetic, holistic, and equitable approaches to diabetes care.

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