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Review article

Animal models in biomedical research: Relevance of *Drosophila melanogaster*

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ABSTRACT

Animal models have become veritable tools in gaining insight into the pathogenesis and progression of several human diseases. These models could range in complexity from *Caenorhabditis elegans* to non-human primates. With the aid of these animal models, a lot of new knowledge has been gained about several diseases which otherwise would not have been possible. Most times, the utilization of these animal models is predicated on the level of homology they share with humans, which suggests that outcomes of studies using them could be extrapolated to humans. However, this has not always been the case. *Drosophila melanogaster* is becoming increasingly relevant as preferred model for understanding the biochemical basis of several human diseases. Apart from its relatively short lifespan, high fecundity and ease of rearing, the simplicity of its genome and lower redundancy of its genes when compared with vertebrate models, as well as availability of genetic tool kit for easy manipulation of its genome, have all contributed to its emergence as a valid animal model of human diseases. This review aimed at highlighting the contributions of selected animal models in biomedical research with a focus on the relevance of *Drosophila melanogaster* in understanding the biochemical basis of some diseases that have continued to plague mankind.

1. Introduction

A disease is a condition, state, or process that affects the body and jeopardizes not just the physical structures and functions, but also the overall health and well-being [1]. A disease may also be described as a condition in which human ability deviates from the biomedical norm or the typical state [2]. Diseases occur due to disruptions in the structure or function of parts of an organism caused by failure of the adaptation mechanisms of the organism to effectively combat the stresses and stimuli it is exposed to Ref. [3]. Each disease is distinct and has a range of indications, symptoms, and consequences. Recent research on the pathogenesis of numerous human diseases has revealed that aberrant mechanotransduction as well as deviations in the mechanical and structural characteristics of cells are implicated in the genesis of these disorders. This leads to the disruption or deregulation of the molecular systems by which

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cells perceive mechanical impulses and translate them into biochemical responses, which in turn causes the collapse of physiological activities in sick states [1].

Animals have been used in studies for a very long time, since the fourth century B.C. For instance, William Harvey described the circulatory mechanism of the blood using animals in the 1600s. Emil von Behring and Louis Pasteur also employed animal models to validate their theories [4]. Tissue culture research and cell-based tests are two other methods utilized to look into the mechanisms behind diseases and offer potential treatments. Although these models can yield valuable insights, they are unable to account for diverse physiological circumstances and the intricate relationships between distinct cell types found in tissues and organs, which is obtainable in animal models [4].

Experimental animal models have contributed immensely to a better understanding of disease mechanisms and have been effectively used to screen novel bioengineered, pharmaceutical, or herbal treatments that may have the potential to treat human patients for diseases ranging from multiple sclerosis to rheumatoid arthritis. However, in spite of the successes recorded in animal studies, over 80 % of such screened drugs fail in human trials [5].

2. Animal models in biomedical research

Animal models, which are usually utilized on the basis of comparative medicine, have contributed enormously to biomedical research by providing better understanding of both physiological and pathological processes [6]. Animal models can be broadly classified into two categories, spontaneous and induced. Spontaneous models include normal animals with phenotypes that are similar to humans or atypical members of a specie that develop differently due to spontaneous mutation(s). On the other hand, induced animal models are those that are generated as a result of surgical, chemical, genetic, or other interventions, which alter their typical physiology [7].

Mammalian models, particularly mice, rats, rabbits, and guinea pigs, are regarded as standard models used for a wide range of disease modelling. This was apparently because of the higher similarity level between their genomes and that of humans [8]. For instance, about 95 % of the 30,000 genes present in mice, rats and humans, are similar [9]. However, with rising concerns relating to animal welfare and campaigns for animal rights, the use of these mammalian models began to wane. This necessitated the search for non-mammalian alternative model organisms [10]. Species lower on the phylogenetic tree, such as the nematode (*Caenorhabditis elegans*), the fruit fly (*Drosophila melanogaster*), the zebrafish (*Danio rerio*), and the frog (*Xenopus laevis*), are now also frequently used as models for human diseases. Larger animal models, such as dogs, pigs, sheep, and non-human primates, which more closely resemble human anatomy and physiology, are often desirable for translational studies in cardiovascular, metabolic, genetic (including rare disease), and neurodegenerative diseases (ND) [11].

It is often necessary to use models that replicate part or all of the reported pathologies while studying human disease. In addition to helping to better understand the genetic causes of disease and its phenotypic consequences, the use of disease models offers a platform for testing possible prophylactic, therapeutic and surgical strategies [12,13]. It is worthy of mention that each animal model has distinct advantages over the others. Therefore, the choice of model is a function of the features of the disease being studied and the scientific question to be answered. In several instances, more than one animal model may be required for a better understanding of the disease being studied [14].

Some of the frequently used animal models in biomedical research are discussed in the next section of this review article.

2.1. Mouse

The most popular model organism for studying human diseases is the mouse. They were not initially regarded as good models because preclinical research in mice had not always resulted in human treatments [15,16]. An important factor that tilted the balance of preference in favour of mice over rats was availability of genetic manipulation techniques for mice, especially around the time when the first knockout mouse was achieved and reported in 1987 [17].

For practical and financial reasons, scientists greatly benefit from their small size, quick reproduction, and simplicity of handling. Furthermore, when simulating human disorders involving the production of oxidative stress (i.e., aging, inflammation, and neurodegeneration), it is important to consider that mice create reactive oxygen species more readily than humans [18]. The transferability of the acquired knowledge in mice is restricted by variations in the mechanical and electrophysiological functions of the heart as well as in the makeup of electrical and contractile proteins. Furthermore, two significant drawbacks are the small size, which makes using organs and performing surgery difficult, as well as the rapid heart rate and high metabolic rate [19].

2.2. Rat

Laboratory rats were considered essential and preferred model organisms in the last 30 years of the 20th century. However, the advent of transgenic technologies and gene-targeting in mice made rats lose popularity as model animals [20]. Like mice, using rats as disease models is economical in that they grow to adulthood rapidly, they have short lifespans, they are relatively small in size and require little space or resources to maintain [9]. However, rats are preferred as models in some specific cases. For example, in the field of cancer research, particularly mammary cancer research, it has been established that human and rat carcinomas exhibit comparable histopathological characteristics and development. Additionally, rat mammary tumours are heavily dependent on hormones for both induction and growth, making them similar to human breast tumours [21].

In terms of size, rats are around ten times bigger than mice. This means they would require more space and test compounds than

mice. However, their relatively larger size makes them more amenable to surgical procedures such as catheter implantation necessary for research on addiction [22], and they are more appropriate for time course experiments and serial blood draws. Their size also makes them more suitable to surgical procedures and manoeuvres within the thoracic cavity which include induction of myocardial infarction and evaluation of cardiovascular indices (e.g. blood pressure) via implantation of telemetry devices in the aorta, which has a wide enough diameter to allow the flow of blood around the blood pressure sensor [20]. All these also make them a better alternative for studying cardiovascular diseases when compared with mice [23,24].

In recent times, rats are becoming more relevant in the study of neurodegenerative disorders because of ease of handling and less aggression towards members of the same species [17,25]. Availability of rat lines that bear and overexpress genes that cause NDs in humans, such as Alzheimer's disease (AD), Huntington's disease (HD) and Parkinson's disease (PD), has also contributed to wide utilization of rats for research on neurodegenerative disorders. Some of the transgenic rat models of for NDs include McGill-R-Thy1-APP and TgF344-AD for AD, PINK1 knockout and DJ-1 knockout for PD and tgHD and BACHD for HD [26]. Several behavioural tests which are presently used in rodents were originally developed in rats. Thus, rats perform better in cognitive tests such as Morris water maze, decision-making task, because they learn faster than other rodents [27,28]. Moreover, studies have shown that rats, like primates, have metacognition. This is especially applicable in impaired metacognition which is characteristic of Alzheimer's disease (AD) and other dementias [29]. Furthermore, because rats have larger brains than mice, their enhanced spatial resolution makes neuroanatomy and neurobiology imaging studies more successful in rats when compared with mice [23].

2.3. Pig

One of the most popular domestic animals worldwide is the pig. Pigs develop quickly, have short generation intervals, have big litter sizes, and use conventional breeding practices in comparison to other livestock and primates. They are increasingly being used as animal models for human diseases due to these benefits as well as similarities in their genomes, diets, anatomical and physiological traits, and body proportions between humans and pigs [30].

Due to the fact that the cytochrome P450 protein family, the most significant class of drug-metabolizing enzymes, varies significantly between rodents and humans in terms of substrate selectivity and number of distinct cytochrome P450 subfamilies, rodents are not very good model organisms for evaluating the effects of medications that go via hepatic first-pass metabolism. However, pigs are a more promising model of human drug metabolism involving the cytochrome P450 protein family [31].

The research and treatment of human diseases have benefited greatly from the availability of pig models for several illnesses, including metabolic disorders (e.g. type 2 diabetes, hypertriglyceridemia and non-alcoholic fatty liver disease), neurological disorders (e.g. AD, PD and HD), cardiovascular (e.g. atherosclerosis and myocardial infarction), and genetic conditions (e.g. cystic fibrosis, breast cancer and Duchenne muscular dystrophy [30]. A few surgical and non-surgical procedures often used in human medicine, such as catheterization, heart surgery, valve manipulation, endoscopy, and broncho-alveolar lavages, can be performed on pigs by selecting the appropriate breed and age. In most other animal models, these treatments are extremely challenging or impossible to carry out [32].

A comparison of human, pig and mouse genomes revealed that the pig genome has a higher similarity to human sequences and has more ultra-conserved areas when compared with the mouse genome [33]. Overall, it was shown that pigs and humans have a higher degree of sequence homology than rodents. These findings suggest that using pigs as models to research human diseases that relate to the immune systems, such as cancer, is feasible [33].

2.4. Rabbit

Studies on the European rabbit *Oryctolagus cuniculus* have been useful in developing and evaluating therapeutic humanized polyclonal and monoclonal antibodies, as well as in clarifying many basic elements of antibody structure and diversification mechanisms [34]. Due to their sensitivity to infection and the etiology of several infectious diseases being comparable to that of humans, rabbits have been used as a major experimental model for human diseases [35]. Intradermal inoculation of rabbits with microorganism such as *Treponema pallidum* and intrathecal administration of rabbits with *Mycobacterium tuberculosis* (MTB) or *Mycobacterium bovis* (MBO), respectively resulted in pathologies of syphilis and tuberculosis [36–38]. Moreover, transgenic models of monogenic cardiac diseases and spontaneous hypercholesteremia have been developed in rabbits, and they have improved the understanding of atherogenesis and metabolism of lipoproteins, as well as development of drugs, such as statins [39,40].

Despite being a popular animal model for molecular immunology research in the late 1980s, rodents gradually displaced rabbits in the years that followed. Reduced maintenance costs, small size, availability of inbred strains, ease of breeding, short reproductive cycle, large number of progenies, wide availability of commercial immunological reagents, and availability of numerous knockout (KO) and transgenic models are some of the reasons why rodents, such as mice, are being used more often in place of rabbits [41,42]. However, due to their small size and phylogenetic characteristics, mice are not always suited for investigations, and the causal mutations resulting in human disease sometimes do not generate similar pathologic alterations in mice [43]. On the other hand, due to its intermediate size and evolutionary closeness to primates, the domestic rabbit has garnered increased interest in biological and pharmacological research in recent years, particularly in cardiovascular illnesses. Rabbits are particularly well-suited as an animal model for cardiac disease research because, in contrast to rodents, their electrical, mechanical, and structural cardiac features are more similar to the human heart [44].

2.5. Zebrafish

It was discovered that 70 % of human genes have zebrafish (*Danio rerio*) orthologues and that the zebrafish and human genomes had a great deal of similarity [45]. This orthology and similarity between the genomes of zebrafish and humans have made zebrafish a key study model to comprehend human disease-related genes and the numerous benefits associated with laboratory manipulation [13]. They have been used in the study of human diseases like epilepsy, osteoporosis, amyotrophic lateral sclerosis (ALS), inflammation, atherosclerosis, autism spectrum disorder, heart failure, type 2 diabetes mellitus, sensorineural hearing loss, enteric nervous system disease, and cancer research [46].

Zebrafish are less expensive than mice and are a simple tool for quickly producing a transgenic animal model. They are widely used because of their affordability, high fecundity, quick generation times, outward development, transparency of the embryonic stages, and simplicity in genome alteration. Because of these characteristics, researchers now have access to a vertebrate model that offers previously unheard-of possibilities for real-time biological process imaging as well as genetic and medication testing [46].

Fluorescent proteins carried by transparent zebrafish enable real-time imaging of particular cells. With the aid of these tools, researchers may track and monitor certain cells and provide a spatiotemporal analysis of gene expression. The zebrafish is therefore a good option for tracking transgenic malignancies from the point of commencement to the point of metastasis and transplantation [47]. All the benefits of zebrafish notwithstanding, some drawbacks to its utilization in modelling human diseases include the significant variance in brain, heart complexity, respiratory and reproductive systems between it and humans. It is therefore pertinent to be cautious in establishing disease parallels between zebrafish and humans [48–50].

2.6. Round worm

Caenorhabditis elegans (round worm) is a nematode worm that has become an effective and attractive model animal because of its minimal requirements for growth and nutrients, production of large number of progenies within a short reproduction cycle via self-fertilization (because they are mostly hermaphrodites), and ease of handling. *C. elegans* has been extensively studied, as it was the first multicellular organism to have its genome sequenced [51]. Determination of the cell lineage map of *C. elegans* which gave insights into control of apoptotic processes, highlighted the fact that stochastic events determine cell life and death. This idea has been confirmed in mammals [52]. Lineage tracing also helps in appreciating physiology, pathology as well as factors responsible for cell-fate decisions [53].

To underline the relevance of *C. elegans* in biological research, several Nobel prizes have been awarded to researchers working with it [54]. Even though *C. elegans* has only about 65 % homologs of human disease-causing genes, its transparent nature up till adulthood has made it a relevant model organism for research. This enables direct observation of several life processes in *C. elegans* [54,55]. Moreover, the transparent nature of *C. elegans* allows the utilization of green fluorescent proteins (GFP proteins) to observe particular cells, neurons and synapses in a living animal [56]. The round worm has a simple genome with just about 302 neurons and an accurately depicted and well elucidated connections [55]. This has facilitated the identification and screening of genetic modifiers and therapeutic compounds that inhibit neurodegeneration, some of which have been found to be efficacious in mammals [57,58]. The expression of variants of human genes in *C. elegans* has made it possible not only to study these genes and their contributions to fundamental cellular processes, but to also have an understanding of their likely roles in human cells [59]. For instance, the expression in worms of *presenilin-1*, which is linked to early onset Alzheimer's disease, assisted researchers to elucidate the likely cellular mechanism that involves Notch signaling [60].

It was probably the determination of the 'longevity gene' in *C. elegans*, suggesting a genetic undertone to aging, that boosted its relevance as an excellent model of aging research. The discovery of the relevance of *daf-23, daf-2 and daf-16* genes to aging in *C. elegans*, and their homologs in mammals, which are linked to insulin/insulin-like growth factor signaling pathway further underlined the importance of *C. elegans* as an excellent model for aging [61,62].

In spite of its benefits, the unavailability of several systems that are physiologically relevant in humans, such as the adaptive immune system, blood transport system, blood-brain barrier and DNA methylation, are not found in *C. elegans*. In addition, unlike in humans, length of the telomere is not connected to aging in *C. elegans*. All these are some of the limitations to using *C. elegans* to model human diseases [63–65].

2.7. Fruit fly

Drosophila melanogaster (fruit fly), an arthropod, is a member of the *Drosophilidae* family of dipterans, which are insects that belong to an order that includes genuine flies or two-winged insects. They are one of the most researched eukaryotic species of fruit fly that has significantly advanced several fields of biology. *Drosophila* is becoming more valued as a helpful model organism for human diseases [66]. The diseases include neurodegenerative diseases, cardiovascular diseases, inflammatory diseases, infectious diseases and metabolic disorders [67]. According to comparative genomic analyses, about 75 % of the human genes linked to various disorders is conserved in *Drosophila* [12]. This has facilitated the understanding of various aspects of an increasing number of human diseases [68]. Even though the fruit fly is frequently seen in the wild loitering around vineyards and orchards, and its name suggests that it feeds on fruits, the fruit fly actually feeds on yeast that develops on fruits, and not the fruit itself [69].

Drosophila has been used as a biological model since about a century ago, and its use has promoted the advancement of genetics and other related sciences [67]. Within this period, *Drosophila* research has yielded a number of groundbreaking findings that have improved human health. One of the significant contributions of *Drosophila* is the discovery of Thomas Hunt Morgan, that genes are

located on chromosomes. This serves as the foundation for contemporary genetics [68]. Morgan significantly improved the idea of inheritance initially put out by Gregor Mendel (much before it was ever recognized that DNA constitutes the genetic material). For his research on the part of chromosomes in inheritance, he was awarded the 1933 Nobel Prize in Physiology or Medicine. Moreover, Hermann Muller, a trainee of Morgan, was awarded the 1946 Nobel Prize in Physiology or Medicine for his discovery in the 1920s, using *Drosophila*, that x-rays can break chromosomes and significantly enhance the pace at which genes mutate [70]. It was later discovered that *D. melanogaster* genome contains about 14000 genes on four chromosomes, much less complex when compared to humans and several other animal models [71]. In total, eight Nobel prizes have been won by researchers working partly or wholly on *Drosophila* [72].

Fruit flies are highly fecund, with the females laying up to 100 eggs a day for up to 20 days. They also have a short lifespan, as the entire growth process from egg to a fully grown adult fly takes roughly 10 days at 25 °C [73]. The life cycle of *Drosophila* is in four stages. After fertilization, the egg, which is the first stage, survives for around a day. After then, a larva hatches and feeds nonstop for the next five days to continue developing. The next stage is pupation, which lasts for about four days and produces a fully grown fly [74]. During the pupa stage, most tissues that are unique to the early embryo and the larva are removed [75]. Groups of cells known as imaginal discs that have been set aside since early embryonic development give rise to the adult tissues (such as the wing, leg, and eye). For the most part, adult tissues in *Drosophila* do not regenerate, just like in humans [70,76]. *Drosophila melanogaster* adults have intricate and sophisticated systems, possessing homologs of the lung, heart, gut, kidney and reproductive system in mammals [67].

Because of their low maintenance cost, large progeny numbers, short generation interval and ease of handling and genetic manipulation, *Drosophila* are highly valued in the laboratory [77]. They have become a veritable tool for scientists to elucidate several fundamental mechanisms underlying human diseases such as rare Mendelian diseases, neurodegenerative disorders, and cancer, as well as decoding the fundamental mechanisms underlying numerous essential biological processes, such as development, nervous system development, function, and behaviour [12,78]. *Drosophila* has also enabled the establishment of the molecular processes of gene activity at a speed and resolution not possible with other animal models [68].

D. melanogaster is currently used as a model in toxicology to carry out mechanistic studies on a number of priority environmental contaminants and toxicants because its use in experimental toxicological studies complies with extant regulations [79]. Because of their brief biological life cycle, fruit flies can be used for toxicological studies covering the period from development to adulthood [12]. Ultimately, the adaptability of this organism and the understanding of its genome have allowed for the execution of extensive pharmacological research to discover novel medications and gain insight into the connections between chemicals and genes [80].

3. *Drosophila melanogaster* as an excellent disease model

The homologies between the genome of *D. melanogaster* and that of humans underlines its usefulness as a suitable model to appreciate the etiology and progression of diseases, as well as general biology. Just about 60 % identity exists in homologs between mammals and fruit fly at the level of nucleotides or proteins [81]. However, identity between conserved functional domains can be as high as 80–90 % [71]. To further support its credential as a unique model for studying diseases, the fruit fly could be seen as several model organisms, with all of them possessing distinct benefits, depending on the stage of the development. For instance, the embryo is utilized mostly in basic studies on development which examine pattern formation, determination of cell fate and development of neurons. The larva, especially at the third instar stage, usually finds application in the study of processes involved in organisms' physiology and development [82].

Drosophila is a model organism that is genetically amenable, and this has made it an attractive model for investigating gene functions and their implication in several processes that have both medical and economic importance. An important tool for making targeted genetic manipulation in *Drosophila* leading to generation of unique disease models, is the GAL4/UAS system. GAL4 is a protein encoding 881 amino acids that was identified in *Saccharomyces cerevisiae* where it functions as a regulator of genes induced by galactose [83]. The GAL4 operates via an upstream activating sequence (UAS) that is present in the promoters of regulated targeted genes. Even though GAL4 is not known to have any effect in flies, and no endogenous *Drosophila* gene has been identified as being activated by it, GAL4 activates transcription in *Drosophila* in transgenes carrying the UAS sequence in its promoter regions. Transgenes are transferred by crossing parent flies with the UAS-target gene or the Enhancer-GAL4 gene, resulting in progeny that carry the triggered target gene [84]. This opportunity has been exploited extensively in *Drosophila* for genetic studies and investigating functions of genes [85].

3.1. *Drosophila disease models*

D. melanogaster has been used as a model organism in multiple experiments, not just genetic research. The disease models include.

3.1.1. *Immune system related diseases*

Like other insects, *D. melanogaster* depends exclusively on the innate immune response, thereby circumventing the changeability of the adaptive immune response [86]. In *Drosophila*, three major signaling pathways are recognized to control the humoral immune response genes after infection. They are the Toll, immune deficiency (imd) and JAK/STAT pathways. While the Toll and imd pathways regulate most of the immune genes, the JAK/STAT pathway is involved with inducing the transcription of genes of proteins that contain thioester, as well as Turandot genes, both of which are involved in the defence of *Drosophila* against pathogens [86,87].

The discovery of the mammalian toll-like receptor signaling pathway, for which the 2011 Nobel Prize in Physiology or Medicine was awarded to Dr Jules Hoffman, was a corollary to the studies on *Drosophila toll* mutant [88,89]. A defining feature of the *Drosophila*

humoral immunity is the synthesis of antimicrobial peptides (AMPs) into the hemolymph by the fat body [90]. The cell mediated aspect of *Drosophila* innate immunity is mediated by immune cells collectively called hemocytes, which circulate in the hemolymph. The hemocytes are differentiated into other cell types such as plasmatocytes, crystal cells and lamellocytes, based on their immunological roles and structure [91].

Drosophila melanogaster has been utilized in several ground-breaking research aimed at elucidating host-pathogen relationship involving several pathogens including human immunodeficiency virus (HIV), Zika virus, Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV), Epstein Barr virus, *Vibrio cholerae*, *Pseudomonas aeruginosa* and *Salmonellae enterica* [92]. *Drosophila* has also been used to investigate innate immune responses, especially the confirmation that the innate immune response might also have memory. It is suitable as a model to study the innate immune response due to the presence of homologs of conserved genes implicated in causing disease, as well as other conserved features such as transcriptional regulators, signaling pathways and immune cascades, that it shares with vertebrates [93,94].

It was earlier reported that an initial exposure of *Drosophila* to *Streptococcus pneumoniae* at a non-lethal dose or the heat-killed form of the bacteria brought about protection against a subsequent exposure to the lethal dose of the bacteria. It was discovered that this protection, which was mediated by the Toll pathway and phagocytes, lasted the remaining part of *Drosophila* life. These observations confirm that like the adaptive immune response, the innate immune response also has memory [95]. Other research however produced contrary results, where several heat-killed bacteria such as *Salmonella typhimurium, Mycobacterium marinum* and *Listeria monocytogenes*, did not bring about protection against subsequent infections, either to the same pathogens or to *S. pneumoniae* [95].

In a study using *Drosophila*, it was first discovered that lethal factor (LF) and edema factor (EF), the two bacterial proteins responsible for anthrax (*Baccilus anthracis*) pathogenicity, work in synergy such that absence of one significantly reduces the virulence of the pathogen [92,96]. Other pioneering studies using *Drosophila* revealed that both LF and EP exert their pathogenicity via both the Notch and MAPK signaling pathways [97,98].

Using the *Drosophila*, Hleihel and colleagues elucidated a novel posttranslational modification that may alter the mode of action of Tax1, a transactivator of Human T Cell Lymphotropic Virus type 1 (HTLV-1). HTLV-1 is an oncogenic virus that predisposes to adult T cell lymphoma (ATL), which has a poor prognosis. Their study first showed that over-expression and covalent conjugation of Urm1 (ubiquitin-related modifier 1) with Tax1 changes the subcellular location of Tax1 from the nucleus to the cytoplasm, where it activates the imd pathway downstream to the NF-κB pathway by interacting with the cytoplasmic regulators of the pathway [99].

The usefulness of *Drosophila* in screening and identifying erstwhile unknown target genes as well as pathogenic factors and their pathways, was highlighted by Chan et al. (2007). The authors discovered that over-expression of one of the viral proteins responsible for the effects of SARS-CoV-1 (protein M) in *Drosophila*, led to the rough eye phenotype, associated with augmented apoptosis in the marginal disc of the emerging eye. These effects were countered by over-expression of Pdk1 (Phosphoinositide-dependent kinase 1). It was later discovered that the pro-apoptotic effect arising from over-expression of M was due to its modulation of the degree of phosphorylation of fly Akt1, which is an important kinase in the PKD/AKT pathway, and a known target of Pdk1. The study suggested that pro-apoptotic effect of M in cells is due to its ability to regulate the Pdk1-Akt1 axis of the PKB/ATK pathway. Phosphorylation of Akt1 has been earlier identified as a core event in the Toll arm of the innate immunity pathway in *Drosophila*, that stimulates apoptotic cell death mediated by caspases [100,101].

3.1.2. Cardiovascular diseases

Cardiovascular diseases (CVDs) are the leading cause of death globally. These diseases affect either the function or the structure of both the heart and blood vessels. Majority of heart diseases take the form of channelopathies and cardiomyopathies [102]. The fruit fly is regarded as a choice model for studying human cardiac diseases, heart functions and aging, because it expresses cardiac master genes that control heart development and physiology in humans and because genetic tools for manipulating the fruit fly are readily available [103,104]. Moreover, the fruit fly is about the lone invertebrate that has a working organ whose development and function are homologous to the vertebrate heart [105]. The tinman (Tin), the NK2 homebox transcription factor which was discovered in *Drosophila* plays a vital role in the specifying the fates of cardiac cells. The gene functions as a target for cardiogenesis-inducing signals. Discovery of tinman in flies prompted efforts leading to the discovery of its homolog (homeobox gene Nkx2-5) in chordates, urochordates and humans, where it serves essentially the same function [106,107]. Due to the short lifespan of fruit fly and its aging process that is well characterized, it has become increasingly useful in modelling long-term deviations in heart function that can be followed over the course of a lifetime [108].

Congenital heart defects (CHD) are diverse anomalies of the heart or the great vessels. It has a prevalence of about 0.8 % of all newly born babies. In spite of all efforts, the genes responsible for about 75 % of all CHD cases are not known [109,110]. Various methodologies have been developed to examine heart anatomy and function in *Drosophila*, revealing parallels between flies and human heart development and function, including malfunction when studying genes associated with diseases and their variants. Overall, these characteristics make the fly a versatile model system capable of screening hundreds of potential CHD genetic variations quickly and affordably [111,112]. In one study, RNAi-based functional screen of 134 genes related with CHD showed that more than 70 genes were involved in *Drosophila* heart development, establishing their causality. One particular hit was *WD repeat domain 5* (*WDR5*) with silencing its fly heart homolog (*Wds*) leading to total developmental lethality, accompanied with aberrant heart structure in the late larvae stage of the fly, decreased cardiac myofibres and elevated deposition of pericardin. Conversely, overexpressing wildtype human *WDR5* in *Wds* deficiency flies restored the cardiac phenotype [113]. Another previous research using *Drosophila* has also helped to recognize the genes involved in methylation of histone H3K4 and H3K27 as new genes responsible for CHD [113].

The fruit fly model has helped to understand the heart malfunctions that accompany gradual degeneration in patients with muscular dystrophy. Two forms of muscular dystrophy (Duchenne and Becker) are linked with cardiomyopathy, which inhibits

efficient pumping of blood by the heart [114]. Two different forms of fly dystrophin gene, which is the causal gene for the structural protein implicated in muscular dystrophy, are also expressed in adult myocardium, which is an indication the dystrophin gene is likely to be involved in fly cardiac function [105]. Calcium handling is a very important regulatory mechanism for appropriate cardiac contraction and relaxation. The level of both extracellular and intracellular calcium is maintained within narrow limits by several genes, including the ryanodine receptor (RyR) and sarcoplasmic reticulum calcium ATPase (SERCA) [115,116]. It was earlier reported that reduced RyR expression in *Drosophila* is associated with poor calcium handling, an observation that was confirmed in vertebrates [117]. In addition, mutations in *Drosophila* sarcolamban, a SERCA-interacting protein, were found to be characterized by changed rhythmic contractions as a result of disturbed calcium handling. These findings suggest that the functions of several genes that contribute to calcium handling within cardiomyocytes are conserved in *Drosophila* and mammals [118].

3.1.3. Cancer

The biochemical and genetic foundations of human cancer have been extensively studied using *Drosophila melanogaster* [119]. The characteristic hyperproliferation of cancer can result from the *Drosophila* cell cycle escaping the normal regulation system. Numerous oncosuppressor genes that control cell division and differentiation have been found by simulating human tumours in *Drosophila* [120]. The characteristics of the fly's tumours are similar to those of humans: abnormal cell shape, skipped apoptosis, autonomous proliferation signals and expansion, and metastasis [120]. Part of the functional homologs of disease-causing genes shared by humans and *Drosophila* include genes related to the cell cycle, differentiation, migration, polarity, adhesion, and apoptosis, which are all well implicated in cancer [121,122].

The reduced genetic redundancy in *Drosophila* compared to mammals is the reason these genes are found at a lower frequency in *Drosophila*. Thus, fewer genes need to be altered to provide a sensitized condition for drug screening, with associated benefits for drug discovery. These features and availability of genetic toolkits for modifying gene expression has made it possible to create complex *Drosophila* genotypes and phenotypes [123]. As a result, *Drosophila* has the advantage of the host-tumour milieu and can represent the cancer state more accurately than conventional in vitro cell culture methods [119].

Since humans and *Drosophila* have different anatomy, not all cancer forms can be studied using this system. *Drosophila* can therefore be a more useful screening tool for specific cancer types than in vitro cultures, even though they might not completely replace whole organism mammalian models [123]. FDA-approved non-cancer and anticancer medications that meet certain genetic parameters can be screened by a high-throughput screening process using *Drosophila* cancer models that are either tailored to a patient's genotype or specific to a particular cancer type [124].

Cell competition is a physiological mechanism in multicellular organisms through which healthy cells (winners) thrive at the expense of their less fit neighbours (losers). It is an essential means by which tissues containing healthy cell population grow, and it also acts as a surveillance mechanism for maintaining the health and functions of tissues. It is worth mentioning that cell competition was first discovered in *Drosophila*, which indicates its contribution to cancer research [125]. Usually, tissues have a means of repressing the growth of oncogenes, such as the polarity-deficient scribble (*scrib*), a process known as epithelial defence against cancer (EDAC) in mammals and tumour-suppressive cell competition in *Drosophila.* Aberrations in the process of cell competition, such as mutation of tumour suppressor genes and oncogenes, coupled with other microenvironment factors such as inflammation, is usually exploited by newly formed tumours which outcompete adjacent wildtype cells. It has been suggested that cell competition might offer a possibility for cancer therapy [125,126].

A recent study using the eye epithelium of *Drosophila* as a model revealed that inositol requiring enzyme-1 (Ire1), one of the three endoplasmic reticulum (ER) stress/unfolded protein response (ER stress/UPR) sensors, plays a pivotal role in determining the outcome of cell competition. The study showed that *Ire1*, whether mutated or hyperactivated promoted the elimination *scrib* clones by activating the processes of apoptosis and autophagy. Moreover, dysregulation in *Ire1* activity in neighbouring healthy cells promoted the survival of *scrib* clones. The outcome of the study suggested that consequent upon further mechanistic *in vivo* studies, *Ire1* could be a viable therapeutic target for cancer [127].

Among all cancers, colorectal cancer (CRC) has the second highest mortality, with about 935,000 deaths in 2020. Activation of oncogenes, inactive tumour suppressors, and mismatches during gene repair are some of the events in the pathogenesis of colorectal cancer [128]. The presence in *Drosophila* of a hindgut and midgut which are functional analogues of the colon and intestine in mammals in an important genetic similarity that makes it possible to successfully model CRC in *Drosophila* which exhibit the features of CRC in humans [129–131].

In a study by Bangi et al. (2016), the likely use of *Drosophila* in personalized medicine was underlined. Using the GAL4/UAS system to selectively mutate flies in genes such as *ras p53 pten apc*, they discovered combination therapies for CRC, which include BEZ235 (the first PI3K/mTOR inhibitor to enter clinical trials) and SC79, (a FDA approved drug for cancer that activates AKT), as well as bortezomib (a protease inhibitor) and BEZ235. They discovered that for these therapies to be effective, BEZ235 has to be the second drug, indicating how critical the order of drug administration affects drug action [132]. The synergistic effect of the compounds in these combination therapies and their mechanism of action was observed in *Drosophila* models, mammalian model and genetically engineered mouse model of CRC [133].

Recent statistics showed that lung cancer accounts for about 1.8 million deaths in 2020, and it has been recognized as the deadliest among all cancer types because it has the highest death rate [134]. About 85 % of all cases of lung cancer are of the non-small cell lung carcinoma (NSCLC) type [135]. Significant similarities exist in the development of epithelial cells of the tracheal system of *Drosophila* and lungs of vertebrates [136]. The branching of the *Drosophila* tracheal system is analogous to that of vertebrate lung [137]. It has been established that overexpression of epidermal growth factor receptor (EGFR) is responsible for about 80 % of all NSCLC cases [138], and that structure wise, the EGFR has an intracellular tyrosine kinase (TK) which is distinctly comparable between *Drosophila*

and humans [93]. Ectopic expression of *EGFR* in *Drosophila* to model lung cancer was utilized in drug screening which culminated in the identification of TK inhibitors (TKI) such as afatinib, ibrutinib and gefitinib [139]. These compounds were found to be effective at preventing lethality in the whole-organism *Drosophila* model. In addition, consequent upon screening of FDA-approved library, bazedoxifene and afatinib were discovered to have synergistic effects which lowered JAK/STAT signals induced by hypoxia, and thereby prevented lethality caused by EGFR [123].

Ewing sarcoma (EwS) is a cancer of soft tissues and bones, usually caused by Ewing's sarcoma breakpoint region 1-Friend leukemia virus integration 1 (EWS-FLI) oncogene. Due to the extreme toxicity of EWS-FLI, it was difficult to generate a genetically modified *in vivo* model of the disease, until a frame-shift variant that retains the oncogenic effect, albeit with no toxicity, was generated in *Drosophila*. Moreover, using genetic engineering, full length and unmodified EWS-FLI has been expressed in *Drosophila*, giving rise to a series of phenotypes which differ on the basis of protein levels of EWS-FLI. The outcome of this study provides an avenue for a better understanding of transcription dysregulation due to EWS-FLI [140].

3.1.4. Diabetes

Diabetes is a chronic disease whose main feature is increased level of blood glucose arising from defects in either β-cell function or insulin action, or both [141,142]. In 2019, it was reported to occupy the eighth position among diseases leading to death and disability combined. In spite of efforts to curtail the rising prevalence of diabetes by 2025, a study by the NCD Risk Factor Collaboration (NCD-RisC) in 2016 projected that the likelihood of meeting this target was below 1 % for women, an even lower probability was reported for men [143,144]. To further underline the danger diabetes poses to humanity, it is a major risk factor for ischemic heart disease and stroke, both of which were reported to be respectively the first and second leading cause of disease burden globally [144].

Drosophila melanogaster has been recognized as a valid model relevant to human metabolic illnesses and diabetes that can be utilized in the field of therapeutic discovery due to advancements in the understanding of glucose homeostasis, metabolic processes, and endocrinology in the fly [67]. The *Drosophila* genome contains genes for seven insulin-like peptides (ILP 1–7) which are homologs of the vertebrate insulin and are produced by the insulin-producing cells in the brain. Among the ILPs, ILP2 has the highest homology to the insulin gene in vertebrates. Several *Drosophila* models have been utilized in the study and understanding of both type 1 and type 2 diabetes, which are the major forms of diabetes. This is due to the fact that insulin signaling in *Drosophila* is evolutionarily conserved [145].

Other factors that made the *Drosophila* a preferred model for studying the insulin signaling pathway in diabetes is the lower redundancy in its genome when compared with vertebrate models, and the availability of sophisticated means of manipulating its genome in a way that is not possible with other models [146]. Decreasing or abolishing the expression of ILPs in *Drosophila* can give rise to type 1 diabetes. Conversely, type 2 diabetes can be generated in *Drosophila* via several modifications, such as dietary manipulations and mutations in the components of insulin signaling pathway downstream of ILPs [147–149].

The potential of *Drosophila* as a model for screening novel therapeutic compounds was established by Lagunas-Rangel and colleagues. They established the hypoglycemic effect of Diprotin A, a compound with dipeptidyl peptidase-4 inhibitory effect, although not an approved drug. Dipeptidyl peptidase 4 (DPP4) inhibitors are a class of antidiabetic drugs that do not have inherent hypoglycemic effects, but act mainly by preventing some substrates from being degraded by DPP4. These substrates include incretins, glucose-dependent insulinotropic polypeptide (GIP), as well as neuropeptides and pituitary adenylate cyclase-activating polypeptide (PACAP) [150]. The hypoglycemic property of Diprotin A was evaluated using Drosophila, and it was discovered that Diprotin A reduced the glucose level in hemolymph of flies without affecting the total protein and triglycerides. This discovery underlines the possibility of using *Drosophila* as a tool for initial screening of compounds with DPP4 inhibitory activity in particular, and other compounds with medicinal value in general [151].

Drosophila was used to screen type 2 diabetes risk genes that are particularly concerned with insulin secretion. Out of the 14 gene candidates screened, three (*BCL11A, SIX3 and PRC1*) were identified to functioning as regulators of β-cell function in humans. Additional studies revealed that loss of *BCL11A* in primary human islets improves insulin secretion. It was subsequently discovered via gene expression analysis that *BCL11A* modulates several genes involved in insulin secretion [152].

The Capa peptides and their receptors (CapaR), usually found in adult animals, are involved in signaling activities that affect the renal tubules, heart and hyperneural muscles, as well as regulating myotropic and diuretic activities. The *Capa* gene codes for a preprohormone which is processed to produce four peptides, in *Drosophila*. The Capa peptides are related to the NeuromedinU (NmU) signaling in vertebrates, both functionally and evolutionally [153,154]. In mammals, the functions of the NmU signaling include regulation of insulin release, coordination feeding and homeostasis as well as gastric acid secretion. Studies with Capa/CapaR in *Drosophila* revealed that fed (*ad libitum* feeding) flies lacking *Capa*R presented with marked hyperglycemia alongside hyperactivation of AKH (glucagon analogue), indicating that Capa peptides may control energy metabolism in flies by modulating AKH. Based on the functional conservation between fly Capa and mammalian NmU, and the fact that in humans, NmU is becoming considered as an endocrine regulator of energy homeostasis, the outcome of this study could lead to more insights on the pathophysiology of metabolic disorders in humans, such as diabetes and obesity [155].

3.1.5. Neurodegenerative diseases

Neurodegenerative disorders are the foremost cause of both cognitive and physical disabilities worldwide, with about 15 % of the world population affected [156]. The number of people affected by neurodegenerative disorders has increased significantly over the last three decades, and the number of people living with chronic NDs is projected to at least double over the next twenty years [157].

Drosophila shares some basic physiological, biological, biochemical, and neurological characteristics with other mammalian species, and such similarities make them suitable for use in biomedical research on NDs like AD and Parkinson's, which are becoming

more common in today's aging population [67]. The *Drosophila* brain, which is compact brain consists of neurons and glial cells that perform similar functions as vertebrates. These features make them very useful in research on NDs [158].

Several hypotheses have been put forwarded regarding the etiology of AD Prominent among them is pathogenic amyloid-beta 42 (Aβ42) aggregation, which is caused by successive cleavage of amyloid precursor protein (APP) (or APP-like in *Drosophila*) by β–site APP cleaving enzyme–1 (BACE1) and γ–secretase, instead of α–secretase [145]. Another major hypothesis is intracellular aggregation of hyperphosphorylated Tau protein, which is probably due to amyloid pathology. Other hypotheses for AD etiology are vascular dysfunction, glia-mediated inflammation, metal ion toxicity, oxidative stress, cholinergic and mitochondrial dysfunction and calcium homeostasis. These hypotheses are interconnected [159].

Drosophila models for AD can be generated via several means including mutations in human disease gene orthologs in *Drosophila*, transgenic forms containing alleles of the genes causing disease in humans and effect of environmental causes of Aβ toxicity [160,161].

Phenotypes of AD can be generated in *Drosophila* by producing amyloid plaques and *Drosophila* amyloid β1-42 by genetic modification techniques like the GAL4/UAS system [162]. While there are no Aβ homologous peptides in *Drosophila*, flies in which human Aβ was expressed exhibited aggregation of amyloid plaques, reduced lifespan, dysfunctional learning and neurodegeneration, all of which are characteristic of AD in humans [158]. In order to replicate neurofibrillary tangles in a similar manner, the GAL4/UAS system can also be utilized to insert R406W, the tauopathy-associated mutation of human tau, into *Drosophila* [67,163].

Drosophila models for AD can help study how metal ions affect Aβ-induced neurodegeneration. Feeding diet supplemented with copper or zinc to Aβ42-expressing flies reduced survival and increased locomotor abnormalities. Food containing metal-chelating compounds inhibited these characteristics [164]. Genetic manipulation of metal homeostasis further supports the importance of zinc and copper levels in Aβ42-induced toxicity [165,166].

Various experimental models of AD have suggested that overactivation of poly(ADP-ribose)polymerase-1 (PARP-1) is implicated in the pathogenesis of AD [167,168]. The molecular basis of PARP-1 involvement in AD was elucidated in *Drosophila* by Maggiore et al. (2022). They reported transgenic fly models of AD had improved climbing ability and extended lifespan due to reduced activity of PARP-1, either by pharmacological inhibition or genetic inactivation. Their study also revealed that treatment of Aβ42-induced AD flies with PARP-1 inhibitors prevented both aggregation of Aβ oligomers, while also modulating the structure and function of chromatin, thereby preventing activation of transposable elements arising from AD [169].

Another progressive ND for which fruit flies have been crucial to pathological development and research is Parkinson's disease (PD). It is a heterogenic condition with numerous etiologies and molecular processes that contribute to neurodegeneration. The disease is characterized by the degeneration of dopaminergic (DA) neurons in the substantia nigra pars compacta in which intraneuronal aggregates known as Lewy bodies, which include the protein α-Synuclein (α-Syn) in combination with others, are commonly observed. *Drosophila* lacks α-synuclein, one of the genes connected to familial Parkinson's disease (PD) [170]. This gene produces a protein that is a part of Lewy bodies, which are linked to Parkinson's disease pathology. Human α-synuclein was effectively injected into *Drosophila* via the GAL4/UAS system to cause neurodegeneration, inclusion formation, and subsequent locomotor abnormalities brought on by α-synuclein toxicity [171]. In order to directly detect neurodegeneration, tyrosine hydroxylase was utilized to label dopaminergic neurones in fly brain slices. Climbing test was then utilized to gauge the locomotor response. The findings supported male sterility, decreased permanence, and abnormalities in flying and climbing [67,163].

It has been established that the ubiquitin/proteasome system (UPS) is dysfunctional in neurodegenerative diseases, leading to accumulation of ubiquitinated proteins [172]. The part of UPS responsible for substrate specificity is the E3-Skp1/Cullin1/F box protein (SCF) ligase system. Previous studies have indicated that S-phase kinase-associated protein 1 (Skp1) is under-expressed in sporadic PD. Knockdown of SkpA, the fly homolog of mammalian Skp1, at adult stage neurons of flies, was reported to elevate protein aggregate and loss of dopaminergic neurons of flies. Its over-expression prevented protein aggregates in α-synuclein-induced *Drosophila* PD model, and also improved survival rate in wild type flies. SkpA was also revealed to interact with a recently identified F box protein, nutcracker (Nut) and with other yet to be identified F box proteins. The study demonstrated the neuroprotective effect of SkpA, and its potential as a target for diagnosing and management of neurodegenerative diseases [173].

The autosomal, dominant genetic condition known as spinocerebellar ataxia type 3 (SCA3, also known as Machado-Joseph disease) is brought on by repeats of the CAG trinucleotide at particular gene loci on chromosomes, which elongate the polyglutamine (polyQ) region of the ataxin-3 protein. All polyglutamine illnesses, such as HD, spinal and bulbar muscular atrophy (SBMA), dentatorubral-pallidoluysian (DRPLA), and other forms of spinocerebellar ataxia, share this aetiological process. The rate of neurodegeneration in HD is positively correlated to length of polyQ repeat [174]. These disorders have been demonstrated in *Drosophila melanogaster* since in 1998 when the first transgenic *Drosophila* model of SCA3 was produced. These flies mirrored characteristics of SCA3, making this model organism useful for future studies investigating the causes of degeneration and neuronal death in SCA3 [163].

In HD, the Huntingtin (Htt) protein has a polyglutamine section of 36 units or more as a result of a trinucleotide repeat [161]. This neurodegenerative condition is inherited in an autosomal dominant manner and is clinically characterized by declining choreic motions over time, along with cognitive impairment and mental problems. Research employing *Drosophila* has yielded findings indicating that the huntingtin protein is typically found in the cytoplasm, while mutant variants are found in the nucleus. Additionally, neurons contributing to the pathophysiology of this disease contain inclusions, which are sizable aggregates of the mutant protein and transcriptional co-activators. *Drosophila melanogaster* has been used to study therapeutic intervention in addition to offering insights into the etiology and pathophysiology of Huntington's disease [161,163].

PolyQ pathology has been associated with inhibition of acetyltransferase enzymes. The expression of polyQ in *Drosophila* is used to generate the fly HD model, which shows similar features to that of humans. A landmark contribution of the *Drosophila* to proteinopahies associated with HD was recorded by Steffan and coworkers. Using fly model of HD, the researchers discovered that activity of histone deacetylase (HDAC) may potentiate polyQ-induced neurodegeneration, a phenomenon that has since been identified in

humans. They also discovered that HDAC inhibitors reversed the observed neurodegeneration in flies and may be relevant in slowing or preventing progressive neurodegeneration observed in HD and other polyQ-associated diseases [175].

4. Drawbacks of using *Drosophila* as disease model

Despite the myriad possibilities provided by *Drosophila* as models for human diseases, some limitations are worth considering. One clear downside of utilizing *Drosophila* models is the possibility that some essential pathogenetic factors are vertebrate-specific and will be overlooked in invertebrate models. Immune system-related illnesses, such as multiple sclerosis, cannot be adequately modeled in *Drosophila melanogaster*. Furthermore, brain infarctions and hemorrhages cannot be studied in *Drosophila* due to absence of blood vessels, while blood cells are primarily restricted to primitive hemocytes [176]. Moreover, it is difficult to conserve *Drosophila melanogaster* strains (e.g. frozen stocks), as they are maintained as living cultures only [166].

5. Conclusion

The plethora of animal models available in biomedical research has no doubt improved the understanding of researchers as regards several aspects of human physiology and diseases. Even though *Drosophila* has been contributing to the advancement of scientific research for about a century, it remains an attractive organism for elucidating both already existing and emerging diseases. It is hoped that in spite of the limitations associated with *Drosophila* models, biomedical research would continue to benefit from both currently available and yet to be identified opportunities that *Drosophila melanogaster* can provide. Furthermore, *Drosophila* models could be considered as part of a combination of multiple animal models that might be necessary for enhanced understanding of conditions being studied. This is especially important for drug approval processes, as suggested by the US Food and Drug Administration that though not compulsory, the effectiveness of drug candidates might have to be demonstrated in more than one animal species in order to get the response that could be reasonably expected in humans [177].

CRediT authorship contribution statement

Olabisi Tajudeen Obafemi: Writing – original draft, Conceptualization. **Ademola Olabode Ayeleso:** Writing – review & editing, Conceptualization. **Olusola Bolaji Adewale:** Writing – original draft. **Jeremiah Unuofin:** Writing – review & editing. **Bidemi Emmanuel Ekundayo:** Writing – original draft. **Monde Ntwasa:** Writing – review & editing. **Sogolo Lucky Lebelo:** Writing – review & editing, Conceptualization.

Ethical statement

Review and/or approval by an ethics committee was not needed for this manuscript because it is a review.

Data availability

No data was used for the research described in the article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviations

AD	Alzheimer's disease
ALS	Amyotrophic lateral sclerosis
AMP	Antimicrobial peptides
APP	Amyloid precursor protein
Aβ42	Amyloid-beta 42
BACE1	β–site APP cleaving enzyme–1
CHD	Congenital heart defects
CRC	Colorectal cancer
CVD	Cardiovascular diseases
DPP4	Dipeptidyl peptidase 4

DRPLA Dentatorubral-pallidoluysian atrophy
EGFR Epidermal growth factor receptor
EWS-FL1 Ewing's sarcoma breakpoint region 1-Friend leukemia virus integration-1
FDA Food and Drug Administration
GFP Green fluorescent proteins
HD Huntington's disease
HDAC Histone deacetylase
HIV/AIDS Human Immunodefficiency Virus/Acquired Immune Deficiency Syndrome
HTLV-1 Human T Cell Lymphotropic Virus type 1 (HTLV-1)
H3K4 Histone H3 lysine K4
H3K27 histone H3 on lysine 27
ILP Insulin-like peptides
IMD Immune deficiency
JAK/STAT Janus kinases/Signal transducer and activator of transcription proteins
MAPK Mitogen-activated protein kinase
MBO *Mycobacterium bovis*
MTB *Mycobacterium tuberculosis*
NCBI National Center for Biotechnology Information
NCD-RisC Non-communicable disease risk factor collaboration
NmU NeuromedinU
NSCLC Non-small cell lung carcinoma
PARP1 Poly(ADP-ribose)polymerase-1
PD Parkinson's disease
RAS Rat sarcoma
RyR Ryanodine receptor
SARS-CoV Severe Acute Respiratory Syndrome Coronavirus
SBMA spinal and bulbar muscular atrophy
SERCA Sarcoplasmic reticulum calcium ATPase
TGF-β Transforming growth factor
TK Tyrosine kinase
UAS Upstream activating sequence
UPS Ubiquitin/proteasome system
WNT Wingless-related integration site

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