

## Review Article

# Treatment of Obesity-Related Complications with Novel Classes of Naturally Occurring PPAR Agonists

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Received 27 April 2010; Revised 25 July 2010; Accepted 2 December 2010

Academic Editor: Luc F. Van Gaal

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The prevalence of obesity and its associated comorbidities has grown to epidemic proportions in the US and worldwide. Thus, developing safe and effective therapeutic approaches against these widespread and debilitating diseases is important and timely. Activation of peroxisome proliferator-activated receptors (PPARs)  $\alpha$ ,  $\gamma$ , and  $\delta$  through several classes of pharmaceuticals can prevent or treat a variety of metabolic and inflammatory diseases, including type II diabetes (T2D). Thus, PPARs represent important molecular targets for developing novel and better treatments for a wide range of debilitating and widespread obesity-related diseases and disorders. However, available PPAR  $\gamma$  agonistic drugs such as Avandia have significant adverse side effects, including weight gain, fluid retention, hepatotoxicity, and congestive heart failure. An alternative to synthetic agonists of PPAR  $\gamma$  is the discovery and development of naturally occurring and safer nutraceuticals that may be dual or pan PPAR agonists. The purpose of this paper is to summarize the health effects of three plant-derived PPAR agonists: abscisic acid (ABA), punicic acid (PUA), and catalpic acid (CAA) in the prevention and treatment of chronic inflammatory and metabolic diseases and disorders.

## 1. Introduction

During the past two decades, the prevalence of obesity has risen to epidemic proportions in the United States, and current estimates indicate that approximately 67% of the population is overweight and one-third is obese. This burgeoning problem has brought with it numerous health and fiscal concerns. Obesity is associated with a number of chronic diseases such as type II diabetes (T2D), cardiovascular disease (CVD), chronic kidney disease (CKD), nonalcoholic fatty liver disease (NAFLD), obstructive sleep apnea (OSA), gallbladder diseases, and various types of cancers [1], and obesity-related spending is currently estimated at \$147 billion per year [2]. This number has been anticipated to rise to \$344 billion, or 21% of all health care spending, in 2018 if rates continue on their current trajectory [3].

PPARs are the receptors for endogenous lipid molecules (i.e., prostaglandins or hydroxy-containing PUFA such as 12/15-hydroxyeicosatetraenoic (HETE), 13-hydroxyoctadecadienoic (HODE)) molecular targets for drugs against

type 2 diabetes [4–6] and represent promising new targets for the treatment and prevention of inflammatory disorders such as IBD [7, 8]. PPARs belong to the superfamily of nuclear hormone receptors with 48 members identified in the human genome. There are three known PPAR isoforms;  $\alpha$ ,  $\beta$  or  $\delta$ , and  $\gamma$ , which differ in their tissue distribution and functional activity [9]. Functionally, PPARs regulate inflammation, immunity, and metabolism [10]. PPAR activation and expression is controlled by a diverse set of natural and synthetic molecules, including nutrients, nonnutrient endogenous ligands, and drugs (i.e., thiazolidinediones (TZDs) and fibrates).

Activation of the nuclear receptor peroxisome proliferator-activated receptor  $\gamma$  (PPAR  $\gamma$ ) has shown efficacy in the treatment of type II diabetes [11], inflammatory bowel disease [12, 13], colorectal cancer [14, 15], and influenza virus-induced pulmonary inflammation [16]. Thiazolidinediones (TZDs) are highly efficacious in activating PPAR  $\gamma$ , but the key representative of this class of drugs, rosiglitazone (Avandia), is associated with significant adverse side effects,

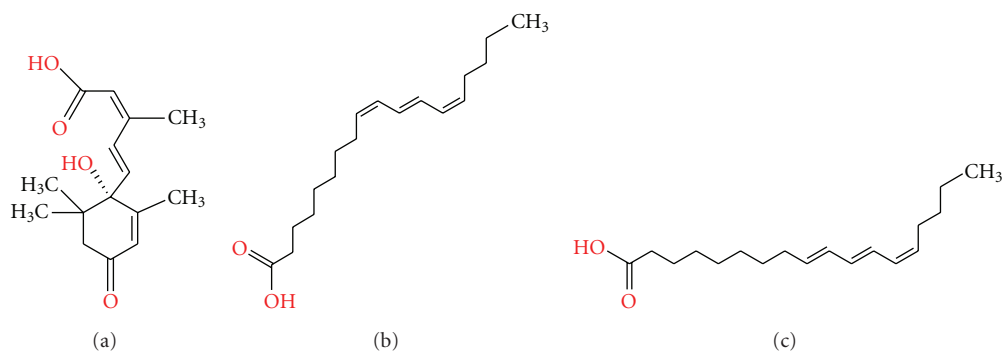


FIGURE 1: Chemical structures of the isoprenoid abscisic acid (a) and the conjugated linolenic acid stereo- or regioisomers punicic acid- (9Z, 11E, 13E-) octadeca-9, 11, 13-trienoic acid (b) and catalpic acid- (9E, 11E, 13Z-) octadeca-9, 11, 13-trienoic acid (c).

including weight gain, congestive heart failure, and fluid retention [6]. Although the results of the recent action to control cardiovascular disease in diabetes (ACCORD) trial did not report side effects associated with the use of the fibrate class of PPAR  $\alpha$  agonists [17], other studies have reported that they can increase the risk for myopathy, cholelithiasis, and venous thrombosis [18]. Therefore, based on the concerns regarding cardiovascular safety of rosiglitazone, in 2010, the European Medicines Agency took rosiglitazone off the market in Europe. Moreover, the Food and Drug Administration restricted the use of rosiglitazone in the United States to situations in which other medications are not effective, thereby minimizing its use. Thus, there is an urgent need to develop novel and safer agonists of PPAR  $\alpha$  and  $\gamma$  as therapeutics for obesity, diabetes, inflammation, and cancer. Our group has already developed a pipeline of naturally occurring compounds that activate PPARs [12, 19–26] and are both efficacious and safe, thereby confirming that in spite of the side effects of some synthetic agonists, PPARs remain valid drug/nutraceutical discovery targets. We have also set up the systems for virtually screening large compound libraries [27]. This paper describes the mechanisms of action of abscisic acid (ABA), punicic acid (PUA), and catalpic acid (CAA) (Figure 1) and their effects in mouse models of obesity, diabetes, and atherosclerosis.

## 2. Abscisic Acid

In 2009, the story of the isoprenoid phytohormone abscisic acid (ABA) and its elusive receptors were selected as runner up for “breakthrough of the year” by Science magazine [28]. This distinction awarded to ABA-research is attributable in part to the importance that ABA holds as a signaling compound. In plants, ABA is involved in numerous developmental and adaptive stress responses, including those related to stomatal opening and closing, pathogen defense, embryo and seed development, germination, promotion of seed desiccation tolerance and dormancy, and general growth and reproduction [29]. Researchers over the past 30 years have identified over 100 loci and numerous second messengers involved in ABA-induced responses, messengers such as calcium, reactive oxygen species (ROS), cyclic nucleotides, and phospholipids [29].

During the past few years, our laboratory and others have been investigating the potential of ABA as a bioactive compound for the prevention and treatment of diseases. In 2007, Bruzzone et al. found that ABA can be produced by human granulocytes and proposed that it may function as an endogenous signaling compound in mammals [30]. The signaling pathway identified by Bruzzone et al. is remarkably similar to that described in plants. The components of the pathway include a pertussis-toxin-sensitive G-protein-coupled receptor on the plasma membrane, cAMP overproduction, protein kinase A- (PKA-) induced activation of ADP-ribosyl cyclase CD38, cADP-ribose generation, and an increase in intracellular calcium [30]. The lanthionine synthetase C-like protein 2 (LANCL2), a protein which shares high-sequence homology to the ABA-binding protein GCR2, was recently recognized as being critical for ABA-induced responses in the mammalian cells [31].

Research in our laboratory has focused on *in vivo* effects of ABA administration. We initially determined that ABA increases the activity of the nuclear receptor peroxisome proliferator-activated receptor  $\gamma$  (PPAR  $\gamma$ ) in 3T3-L1 preadipocytes [22]. Because it has been shown to be an influential protein in a number of cells and tissues integral to glucose homeostasis, uncovering how PPAR  $\gamma$  activation improves the insulin response has been a complex task. In white adipose tissue (WAT), a region which expresses high levels of PPAR  $\gamma$ , TZDs increase the differentiation of new adipocytes, thereby preventing adipocyte hypertrophy and lipid efflux into peripheral tissues [32]. PPAR  $\gamma$  activation also inhibits macrophage and lymphocyte-induced inflammation [33], a hallmark of obesity and its comorbidities, and its presence has been shown to be important in the proper function of key metabolic regions such as skeletal muscle [34], the liver [35], and pancreas [36].

Despite the benefits associated with PPAR  $\gamma$  activation, TZDs are associated with unwanted side effects, such as weight gain, fluid retention, and congestive heart failure, which diminish their appeal as therapeutic agents [6]. Recently, the TZD rosiglitazone was associated with increased risk of myocardial infarction and cardiovascular mortality although another TZD, pioglitazone (Actos), appears to be safer [37]. An objective in our research with ABA was to determine whether it could replicate some of the

beneficial effects associated with PPAR  $\gamma$  activation without causing adverse side effects.

### 3. ABA in Type II Diabetes

Our laboratory's first study with ABA was designed to assess its efficacy in a mouse model of obesity and diabetes [22]. Db/db mice were fed high-fat diets containing a racemic ABA mixture at 0, 100, 200, 400, and 800 mg/kg diet. After a 5-week ABA supplementation, we observed significant improvements in fasting blood glucose at all doses [22]. There were no side effects noted with any of the ABA concentrations. Further testing with ABA continued with the lowest-effective dose measured (100 mg/kg). At this concentration, ABA supplementation significantly improved glucose tolerance, inhibited WAT macrophage infiltration, and reduced tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) mRNA. Expressions of PPAR  $\gamma$  and PPAR  $\gamma$ -responsive genes CD36 and aP2 were also significantly elevated in WAT of ABA-fed mice in comparison to control-fed mice, indicating that ABA mimicked TZDs in their capacity to activate PPAR  $\gamma$  gene regulatory mechanisms in the WAT. Also in line with increased PPAR  $\gamma$  activity, the number of small adipocytes in WAT was increased, and interscapular brown adipose tissue fat pads were greater in ABA-fed mice. ABA-fed mice also had significantly small liver weights [22], an effect that may be due to increased expression of hepatic adiponectin receptors.

We next sought to further dissect the cells and tissues affected by ABA by assessing its effect on the two main fractions of WAT, adipocytes and stromal vascular cells (SVCs). The SVC fraction of the WAT, composed of immune cells, preadipocytes, and endothelial cells and fibroblasts, is a mainly non-energy storing portion of WAT that plays an important role in the tissue's homeostasis. Gene expression analyses revealed that oral ABA supplementation exerted a significantly more substantial affect on the SVCs. Levels of PPAR  $\gamma$  and its responsive gene CD36 were more greatly enhanced in the SVCs than in adipocytes, and SVCs from ABA-fed mice showed a marked reduction (~15-fold) in monocyte chemoattractant protein 1 (MCP-1) mRNA and protein levels [21]. In line with decreased MCP-1, the infiltration of CCR2<sup>+</sup>CD11b<sup>+</sup>F4/80<sup>hi</sup> macrophages into WAT was significantly decreased by ABA [21]. Chemokine receptor 2 (CCR2) is the receptor for MCP-1, and both proteins have been associated with obesity-related inflammation and insulin resistance [38, 39].

To determine whether ABA's effects were dependent on PPAR  $\gamma$ , control and ABA-supplemented diets were fed to tissue-specific PPAR  $\gamma$  knockout mice. The transgenic mice used in this study, PPAR  $\gamma$  flfl; MMTV Cre<sup>+</sup> mice, lacked PPAR  $\gamma$  in all hematopoietic and epithelial cells [12]. After 28 weeks of high-fat feeding, we found that ABA's ability to normalize glucose tolerance and reduce WAT inflammation was significantly impaired in the MMTV Cre<sup>+</sup> mice [21]. There were also no adverse side effects observed with this long-term feeding trial.

Our results show that ABA's antidiabetic effect is mediated through a PPAR  $\gamma$ -dependent mechanism though

*in vitro* studies in human and rat pancreatic islet cells demonstrate that ABA-induced increases in insulin secretion are mediated through cAMP/PKA [40]. Interestingly, recent findings in our lab link PPAR  $\gamma$  activation with the cAMP/PKA signaling pathway. More specifically, by using obese db/db mice, we showed that ABA and the TZD rosiglitazone acted synergistically, rather than competitively, to reduce WAT macrophage infiltration [20]. Further, ABA's *in vitro* activation of PPAR  $\gamma$  in 3T3-L1 preadipocytes was inhibited by the cAMP-inhibitor 2'5' dideoxyadenosine or the PKA inhibitor 14–22 myristolated PKA-inhibitor fragment [20]. There have been previous reports indicating that PKA activation increases PPAR  $\gamma$  activity [41], and together these findings indicate that both cAMP and PPAR  $\gamma$  may be linked to ABA's antidiabetic effects.

### 4. ABA and Cardiovascular Disease

In addition to T2D and obesity-related inflammation, our laboratory has also investigated whether dietary ABA may reduce cardiovascular disease (CVD) risk. When fed to ApoE-deficient mice as part of a high-fat diet for 12 weeks, ABA treatment significantly improved atherosclerosis lesions and atherosclerosis-related hypertension, reduced F4/80<sup>+</sup>CD11b<sup>+</sup> macrophage infiltration and CD4<sup>+</sup> lymphocyte infiltration into the aortic root, decreased aortic root inflammatory lesions, and decreased aortic expression of VCAM-1 and MCP-1 [23]. ABA also increased aortic eNOS expression, both *in vivo* and *in vitro* in human aortic endothelial cells (HAECs) [23]. Short-term (10 minute) stimulation with ABA in HAECs also increased intracellular cAMP and NO release [23], an effect that is likely independent of binding to and activation of PPAR  $\gamma$ .

Despite our consistent anti-inflammatory *in vivo* findings, the effect of ABA on inflammation is somewhat ambiguous. *In vitro* studies from Bruzzone et al. [30], Magnone et al. [44], and Bordrato et al. [45] suggest that ABA has proinflammatory effects as well. In their work which principally dealt with ABA's potential effect on atherogenesis, Magnone et al. show that treatment of monocytes with ABA activates NF- $\kappa$ B and increases MCP-1 and MMP-9 release [44]. ABA also increased aortic smooth muscle cell proliferation and migration and was found at 10-fold higher concentrations in human arterial plaques compared to normal arterial tissue [44]. An alternative explanation is that ABA levels are greater in atherosclerotic plaques as a part of an endogenous regulatory mechanism designed to minimize inflammatory lesion development during atherosclerosis. This alternative explanation would be consistent with our *in vivo* findings in ApoE mice [23], a well established model of atherosclerosis. Ultimately, the discrepancy between both reports as to whether ABA treatment is anti- or proinflammatory highlights an incomplete understanding of the mechanisms of immune modulation by ABA and suggests possible opposing effects depending on cellular and environmental conditions.

Our most recent studies with ABA in a model of colitis suggest that its anti-inflammatory effects may depend on

TABLE 1: Summary of activities of novel classes of peroxisome proliferator-activated receptor (PPAR) agonists.

	Punicic acid	Catalpic acid	Abscisic acid
PPAR $\alpha$ reporter activity <sup>1</sup>	Yes	Yes	No
PPAR $\gamma$ reporter activity <sup>1</sup>	Yes	No	Yes
PPAR $\delta$ reporter activity <sup>1</sup>	No	Unknown	No
PPAR $\gamma$ ligand-binding activity <sup>2</sup>	Yes	Yes	No
PPAR $\gamma$ <i>in silico</i> Docking <sup>3</sup>	Yes	Yes	No
Changes in PPAR-responsive genes <i>in vivo</i> <sup>4</sup>	PPAR $\alpha$ in adipose tissue PPAR $\gamma$ in skeletal muscle	PPAR $\alpha$ in adipose tissue	PPAR $\gamma$ in adipose tissue
Efficacy in tissue-specific PPAR $\gamma$ null mice	Impaired	Unknown	Impaired
PPAR-independent Mechanisms	Modulation of eicosanoid synthesis	Decreases cyclooxygenase-2 expression	Lantionine synthetase component C-like 2, cAMP, and protein kinase A
Proposed utilities	Gut Anti-inflammatory Blood sugar control Immune modulator	Antiobesity Lipid-lowering Anticancer	Systemic anti-inflammatory Blood sugar control Antiatherosclerotic Immune modulator

<sup>1</sup> PPAR  $\alpha$ ,  $\gamma$ , and  $\delta$  reporter activity assays were conducted as previously described [22].

<sup>2</sup> PPAR  $\gamma$  ligand-binding assay was performed using a commercially available competitive tracer displacement kit as previously described [42].

<sup>3</sup> Molecular modeling and docking studies were performed as previously described [27, 43].

<sup>4</sup> PPAR-responsive gene expression was measured *in vivo* as previously described [12].

T cells, and such findings may also hold relevance in its attenuation of CVD risk in ApoE-deficient mice. In the DSS model of inflammatory bowel disease (IBD), we have found that 5 weeks of ABA supplementation significantly improves colitis severity and decreases cellular adhesion molecule and proinflammatory cytokine expression in the colon [46]. The values we observed in this model were much more substantial than those found in the aortas of ApoE-deficient mice. Moreover, these beneficial effects of ABA in this model were impaired in T-cell-specific PPAR  $\gamma$  knockout mice. This outcome occurred despite fully functional PPAR  $\gamma$  in macrophages and epithelial cells; the main cell types involved in the immunopathogenesis of IBD and in the DSS model of colitis. CD4<sup>+</sup>CD25<sup>+</sup>FoxP3<sup>+</sup> regulatory T cells appeared to be important in ABA's anti-inflammatory mechanism in these IBD studies, as well as the protein CTLA-4, which was enhanced on CD4<sup>+</sup> T cells by ABA *in vitro* through a PPAR  $\gamma$ -dependent mechanism [46]. These recent findings in our colitis model corroborate earlier results indicating the importance of immune cells in ABA's anti-inflammatory mechanism and link T cell PPAR  $\gamma$  with ABA's systemic anti-inflammatory effects.

## 5. Conjugated Linolenic Acid Isomers in Obesity-Related Complications

Conjugated linolenic acids (CLnAs) or conjugated triene fatty acids are found as triglycerides in the seed oils of some plants belonging to the Punicaceae, Bignoniaceae, Rosaceae, Curcubitaceae, and Euphorbiaceae families [47]. Glycerides from these plant sources provide an easily accessible source of these unusual types of fatty acids, including but not

limited to punicic (PUA), jacaric acid (JAA) catalpic (CAA), and eleostearic acids (ESA); all of which have demonstrated some promising health effects by acting as dual or pan-agonists of PPARs [12, 25, 26]. Of note, PUA is a conjugated octadecatrienoic acid containing c9, t11, and c13 double bonds that resembles the cis-9, trans-11 conjugated linoleic acid (CLA) isomer, a predominant CLA isomer in nature, ranging from 0.34 to 1.07% of the total fat in dairy products [48, 49]. Interestingly, CLA has shown efficacy both as an immune modulatory nutraceutical [49] as well as a possible antiobesity therapeutic [50]. Although CLA is beyond the scope of the present paper (see [50] for a thorough review), some of the health effects of CLnAs resemble those of CLA.

## 6. PUA in Type II Diabetes and Obesity-Related Inflammation

PUA also known as trichosanic acid is a conjugated triene fatty acid naturally found at high concentrations in the seed of *Punica granatum* (Punicaceae, Pomegranate) [51] and *Trichosanthes kirilowii* [47]. PUA constitutes 64–83 percent of the pomegranate seed oil (PSO) [52, 53], but it also contains minor amounts of ESA, CAA, and JAA [51]. Phytosterols (i.e., beta-sitosterol, campesterol, and stigmasterol) were also found in quite high concentrations in the PSO (4,089–6,205 mg/kg), about 3-4-fold higher than in soybean oil [53]. We recently demonstrated a dose-dependent increase in the ability of PUA to activate PPAR  $\alpha$  and  $\gamma$  reporter activity in 3T3-L1 cells and to bind to PPAR  $\gamma$  and  $\delta$  ligand-binding domain [25]. In line with these *in vitro* findings, we also demonstrated that oral PUA administration ameliorated fasting plasma glucose concentrations and as well as the

glucose normalizing ability during a glucose tolerance test in db/db mice, suggesting that PUA prevents or ameliorates type 2 diabetes. These improvements in disease markers were accompanied with upregulation of PPAR  $\alpha$ -responsive genes in skeletal muscle and both PPAR  $\alpha$ - and  $\gamma$ -responsive genes in intra-abdominal white adipose tissue [25]. Like CLA, PUA also suppressed the expression of inflammatory cytokines such as TNF- $\alpha$  and NF- $\kappa$ B activation. Furthermore, the deletion of the PPAR  $\gamma$  gene from immune cells abrogated the beneficial effect of PUA on glucose normalization and impaired PUA's anti-inflammatory effect, thereby suggesting that PUA ameliorates metabolic and inflammatory changes associated with obesity, in part, through a PPAR  $\gamma$ -dependent mechanism. We have also demonstrated that PUA is safe in acute toxicity studies in rats [54]. We also demonstrated that PUA treatment increased the expression of PPAR  $\delta$  in pancreatic tissue (unpublished observation from our group), suggesting that this isoform may be a potentially interesting mediator of some of the insulin-sensitizing effects of PUA. Based on the phenotype observed during PUA treatment, the response of skeletal muscle could also be PPAR  $\delta$  mediated, although no evidence of such effect is available at the moment.

## 7. CAA in Obesity and Type II Diabetes

Catalpic acid (CAA) is a conjugated triene fatty acid (trans-9, trans-11, cis-13 CLnA) naturally found at high concentrations in the seed of plants in the *Catalpa* Scop. Genus, belonging to the Bignoniaceae family. CAA-producing plants comprise 11 species of trees and shrubs native to East Africa and America, including *Catalpa ovata*, *Catalpa speciosa*, *Catalpa bungei*, and *Catalpa bignonioides* (southern catalpa) of the family Bignoniaceae. CAA constitutes approximately 60% of the oil of the catalpa seed oil. Even though the putative medicinal properties of catalpa trees have been alleged for centuries as a part of popular folklore, little is known about the effects of CAA on chronic conditions afflicting today's developed societies such as obesity and type 2 diabetes. For instance, the biological activities of extracts from *Catalpa bignonioides* have been investigated in recent years [55].

We found that oral CAA administration decreased abdominal fat accumulation, improved glucose homeostasis, increased plasma HDL cholesterol concentrations, increased plasma HDL cholesterol concentrations, and decreases plasma TG levels in mice fed high-saturated fat diets [26]. The lipid-lowering actions of CAA are consistent with the PPAR  $\alpha$  agonistic actions of fibrates [56]. Of note, fibrates increase HDL cholesterol through a PPAR  $\alpha$ -induced transcriptional activation of liver X receptor, a nuclear receptor that increases reverse cholesterol transport through promotion of the ATP-binding cassette transporters ABCA-1 and ABCG-1 [57–59]. Additionally, real time RT-PCR results demonstrated that PPAR  $\alpha$  and PPAR  $\alpha$ -responsive genes are upregulated in WAT of mice administered CAA, whereas PPAR  $\gamma$  and  $\delta$  expression were not significantly affected by CAA in WAT. These data suggest that the metabolic effects

of CAA on glucose and lipid metabolism may be mediated through a PPAR  $\alpha$ -dependent mechanism. In contrast to ABA and PUA that modulate obesity comorbidities (i.e., insulin resistance, diabetes, or systemic inflammation), CAA has a direct effect in reducing adipose tissue accumulation.

## 8. Concluding Remarks and Future Directions

While diet and exercise remain the recommended approaches to prevent and treat obesity and its comorbidities, nutraceuticals and drugs may play a role as adjunct therapeutic interventions for controlling certain aspects of the disease etiopathogenesis. Mounting evidence demonstrates that naturally occurring compounds such as ABA, PUA, and CAA can act on well-established pharmacologic targets such as PPARs and exert their antidiabetic, anti-inflammatory, or antiobesity properties in animal models. In contrast to synthetic agonists of PPARs, these plant-derived compounds are safer and may act through multiple molecular targets. Intervention studies in humans are necessary to determine whether the beneficial effects reported in mice translate into clinical improvements in obese, diabetic, or insulin-resistant individuals.

With regard to the further developments of these compounds, based on the results reported here, CAA will be further developed for antiobesity and lipid-lowering applications, PUA will be developed for regulating blood sugar levels as well as controlling intestinal inflammation, and ABA will be developed for improving insulin sensitivity as a potential safer alternative to TZD and a systemic anti-inflammatory compound. Additionally, we will investigate the possibility of synergistic interactions between these compounds and drugs or other natural products to maximize their efficacy.

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