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A SYSTEMATIC REVIEW ON THE HYPOGLYCEMIC POTENTIAL OF PRENYLATED CHALCONES COMMON IN ASHITABA CHALCONE POWDER (ACP) THAT MODULATES THE NRF2-ARE-KEAP1 PATHWAY

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ABSTRACT

Prenylated chalcones, such as 4-Hydroxy-derricin (4-HD) and Xanthoangelol (XA), are abundant in Ashitaba Chalcone Powder (ACP), have significant hypoglycemic potential. The chalcones acts by upregulating insulin signalling by inhibiting PTP1B, inducing Glut4-dependent glucose absorption via the LKB1/AMPK pathway, upregulating adiponectin and inhibiting α-glucosidase and DPP-IV, differentiating 3T3-L1 preadipocytes into adipocytes via the AMPK pathway, and causing inflammation brought on by hyperglycemia. This review emphasises the Nrf2-ARE-Keap1 pathway-mediated hypoglycemic action of 4-HD and XA

Keywords: Ashitaba chalcone powder, prenylated chalcones, 4-hydroxyderricin, Xanthoangelol, Nrf2, ARE, Keap1, Hypoglycemia, *Angelica keiskei*

INTRODUCTION

Chronic metabolic condition known as diabetes mellitus is characterised by hyperglycemia brought on by inadequate insulin activity. The proliferation of western lifestyles has led to an increase in diabetic patients recently, particularly in Asia. According to reports, people with diabetes have lower levels of the antioxidant defence mechanism, making them more susceptible to oxidative stress **[1]**.

A sizable, clumping, leafy, perennial herb with over 60 species, *Angelica keiskei* is a member of the Umbelliferae family

(Apiaceae) **(Figure 1)**. It primarily grows along Asia's Pacific coast **[2]**. In the Izu Islands and the Miura Peninsula of Japan, this herb is known as ashitaba, and in Korea, it is known as Myeong II Yeob. Both names, which literally translate as "Tomorrow's leaf," reflect the plant's vitality due to its rapid growth and purported regenerative properties within a day of cutting. Ashitaba is also known by the Japanese name Shin-Sun-Cho, which translates to "a precious plant utilised by god" **[3]**.

The word "Angelica" comes from the Latin word for "angel," while the word "Keiskei" comes from the name of Keisuke Ito, a Japanese botanist who is credited with founding modern Japanese botany in the 19th century **[4]**. Since it contains numerous putative bioactive components, such as chalcones, coumarins, and flavanones that promote a multitude of biological functions and may have an impact on human health **[5]**, it has earned the nickname "Elixir of Life." This review summarises data from numerous investigations on the effects of chalcones, which are abundant in ashitaba and which are controlled through the Nrf2-ARE-Keap1 pathway, on antidiabetic activities.

Figure 1: Ashitaba plant

Figure 2: Ashitaba Plant sap

1. Ashitaba chalcone powder (ACP 8%)

The National Health Commission of China officially certified ACP 8% as a new food additive in 2019 and its study is garnering considerable interest for orientations **[6]**. ACP (8%), which was initially discovered in Florae Symbolae Orientali Asiaticae in 1930, is made from the sap of *Angelica keiskei koidzumi* (Kew Royal Botanical Gardens, 2019) **(Figure 2)**. ACP (8%) is produced using ISOELEAT P, a branched cyclodextrin that contains maltose, dextrin, maltosyl cyclodextrin, and > 80% total cyclodextrins obtained from non-GMO (non-Genetically Modified) corn and potato. For 36 months, ACP should be kept at room temperature in an Al bag. Using NOAEL, a safe amount of acceptable daily intake (ADI) of 300 mg ACP per Kg bw per day was discovered **[7]**.

2. Chemical constituents

Xanthoangelol (XAG) and 4-Hydroxy derricin (4-HD), which make up more than 90% of all the chalcones are prenylated at the 5' position **[8, 9]**. Chalcones are the precursors in the production of flavonoids, giving plants their yellow pigment colour by having an open C-ring **[10]**. The main chalcones found in ashitaba is given in the **Table 1**.

Table1: Main chalcones present in Ashitaba

CHALCONES	COMPOUND NAME	PART OF PLANT
1.	4-Hydroxy derricin Xanthoangelol(A,B,C,D,E,F,G,H)	Roots
2.	Xanthokeismin (A,B,C)	Stems
3.	Xanthokeistal A	Leaves

4. Nrf2-ARE-Keap1 Pathway

Nuclear transcription factor E2-related factor 2 (Nrf2) is a basic region-leucine zipper transcription factor that activates a number of antioxidant enzymes, including glutathione-S-transferase, catalase, glutathione peroxidase, and NADPH quinone oxidoreductase **[11]**. When Keap1 (Kelch like ECH-associated protein 1) binds to an E3 ubiquitin ligase complex (Rbx-1) via cullin-3, it promotes the degradation of Nrf2 and functions as a particular inhibitor of Nrf2 **[12]**. Without oxidative stress, Keap1 joins with Nrf2 to form a homodimer in the cytosol, which helps to polyubiquitinate and degrade Nrf2 by the 26s proteosome. As a result, antioxidants, particularly glutathione, are reduced (GSH) **[13]**. The Nrf2-ARE-Keap1 pathway is depicted in the **Figure 3**.

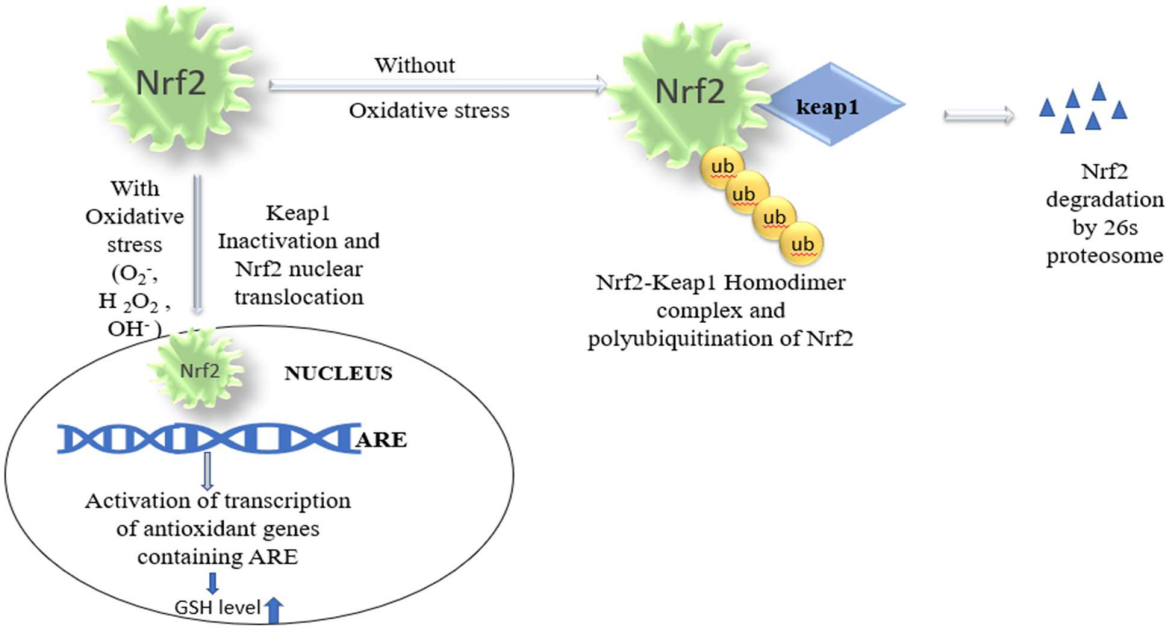

Figure 3: Nrf2-ARE-Keap1 pathway

5. **Role of chalcones in controlling hyperglycemia via Nrf2-ARE-Keap1 pathway**

A crucial prerequisite for the Nrf2-ARE-Keap1 pathway is the dissociation of the Nrf2-ARE complex. Chalcones are thought to be a possible Michael acceptor under oxidative stress. By forming covalent connections with the cysteine residues of keap1, Chalcones could activate this pathway via the Michael addition process. Keap1's ability to cause polyubiquitination and Nrf2 destruction by the 26s proteosome is diminished by this conformational change. It also slows the separation of Nrf2 from the cytoplasmic homodimer complex with keap1 and its nuclear translocation.

Following its release into the cytosol, Nrf2 moves to the nucleus where it binds to ARE (Antioxidant Response Element / Electrophile Responsive Element) in the promoter regions of antioxidant genes **[14]**. This activates the expression of several antioxidant genes that code for enzymes that synthesise antioxidants like glutathione (GSH) intracellularly **[15]**. Therefore, targeting the aetiology of various diseases through Nrf2 activation could be a novel treatment strategy. The **Figure 4** illustrates how prenylated chalcones affect hypoglycemia via the Nrf2-ARE-Keap1 pathway.

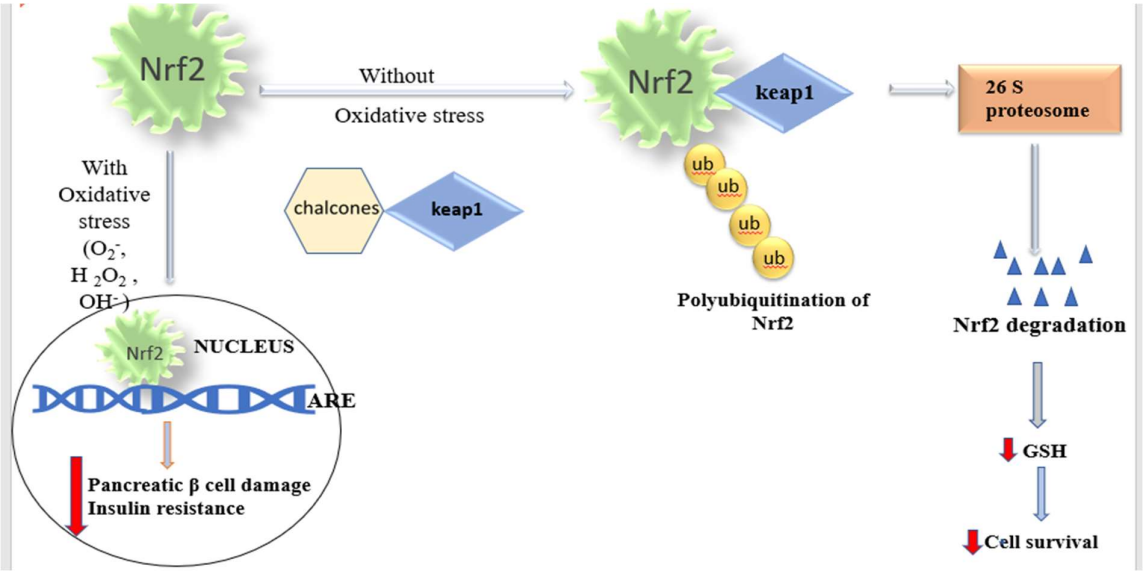

Figure 4: Hypoglycemic potential of prenylated chalcones in ACP via Nrf2-ARE-Keap1 pathway

6. **Diabetes-related characteristics of Nrf2 activators**

In diabetes, Nrf2 activators increase the activity of the glycolytic enzymes Hexokinase (HK), Phosphofructokinase-1 (PFK1), Glyceraldehyde-3-phosphate dehydrogenase (G3PD), and Glucose-6-phosphate dehydrogenase (G6PD) **[16]**.

Nrf2 activators also increase the activity of Protein Kinase-C (PKC), a serine/threonine kinase that controls the development of insulin resistance, poor glucose tolerance, and malfunction of β -cells. By blocking TGFB1, Nrf2 activators reduce sorbitol-mediated ROS generation. The excessive sorbitol synthesis caused by the aldose reductase-induced stimulation of TGFB1 and the increased ROS levels caused by the suppression of Nrf2 expression were evidence of this action **[17]**.

7. The β -cell and the Nrf2-ARE-Keap1 pathway

Nrf2 depletion reduces the expression of cytoprotective antioxidant genes and increases oxidative -cell damage in pancreatic islets of transgenic mice. Reactive oxygen species (ROS) increase the activity of glyceraldehyde 3-phosphate dehydrogenase and reduce ATP synthesis, which inhibits insulin release (GAPDH). Induction of Nrf2 reduces intracellular ROS accumulation, ROS-induced DNA adduct formation, and islet pancreatic β-cell death. Thus, Nrf2 overexpression enhances β-cell's capacity to release insulin.

Reduced expression of antioxidant enzyme genes in pancreatic islets is caused by Nrf2 gene deletion. In contrast, the genetically engineered Keap1 deletion increases the expression of the Nrf2 target antioxidant enzyme in pancreatic islets and genetically activates Nrf2 in pancreatic β-cells. The above results indicate that the Keap1-Nrf2 system does function in pancreatic β-cells **[18]**.

8. Insulin resistance and Nrf2

A fundamental flaw in Type 2 diabetes is insulin resistance, which is characterised by decreased insulin-stimulated glucose uptake as a result of impaired insulin signalling, decreased glucose oxidation, and decreased glycogen formation. Insulin resistance is mostly brought on by oxidative stress **[19]**. It increases cellular glucose absorption and suppresses gluconeogenesis by reducing the expression of glucose 6-phosphate in murine hepatocytes. In response to oxidative stress, Nrf2 increased the expression of proteins such as Heme oxygenase 1 (HO-1), glutathione peroxidase, glutathione S-transferase A1, NAD(P)H, quinone oxidoreductase, and glutamate-cysteine ligase that maintain redox equilibrium and cell viability **[20]**.

9. Hypoglycemic activity of ashitaba chalcone powder (ACP)

9.1 IN SILICO

Alpha-glucosidase and DPP-IV can both be inhibited by XA, according to Diah *et al*. With a binding energy of -7.81 Kcal/mol, xanthoangelol forms a hydrogen bond with Ala 234, an important amino acid residue in the N-terminal N-loop of alpha-glucosidase. With a binding energy of -8.34 Kcal/mol, XA also forms hydrogen

bonds with Glu 205 and Glu 206 at the vast subsite of DPP-IV. Reference medications included sitagliptin, a DPP-IV inhibitor, and acarbose, an alpha glucosidase inhibitor **[21]**. In research using molecular docking simulations, Ring B of the chalcone skeleton has been thought to be anchored in a pocket of PTP1B **[22]**.

9.2 ***IN VITRO***

a) Role of Nrf2 activators in hyperglycemia-induced inflammation

25 mmol/l of glucose caused a 3-fold rise in ROS and other harmful compounds including methyl glyoxal in human microvascular HMEC-1 endothelial cells. The protective effect of Nrf2 activators was lost when Nrf2 was silenced with SiRNA. Studies done in vitro on cell cultures showed that giving Nrf2 activators was essential for reducing the amount of ROS and methyl glyoxal that hyperglycemia-induced inflammation caused. While this effect was not seen in Nrf2 Knockout (KO) mice, newborn cardiomyocytes treated with glucose at concentrations of 20 mM for 6 hours and 40 mM for 18 hours showed a significant increase in Nrf2 mRNA after 24 hours **[23]**.

b) **Role of ACP in differentiation of 3T3-L1 preadipocytes into adipocytes**

Utilizing a differentiation experiment, it was determined if 4-HD/XA in ACP could differentiate 3T3-L1 preadipocytes into adipocytes without activating PPAR-γ. By using a glucose uptake assay where ACP was incubated with differentiated 3T3-L1 adipocytes for an extended period of time and comparing the results with those of insulin incubated with cells for 30 minutes, it was discovered that 4-HD had a higher glucose uptake enhancing activity than XA in ACP **[24]**. To show the inhibitory effect of 4-HD and XAG on adipocyte differentiation via AMPK and mitogen-activated protein kinase pathways, along with downregulation of expression of transcription factors specific to adipocytes, such as CCAAT/enhancer-binding protein-(C/EBP-α), C/EBP-β, and peroxisome proliferator-activated receptor-gamma (PPAR-γ), Zhang *et al*. performed RT-PCR. The underlying mechanism was the phosphorylation-promoted activation of AMPK and acetyl CoA carboxylase during 3T3-L1 adipocyte differentiation. This was followed by a decrease in malonyl CoA synthesis, which in turn led to a decrease in the levels of glycerol-3-phosphate acyl transferase-1 and an increase in the expression of carnitine palmitoyl transferase -1 **[25]**. The role of 4-HD and XA in prevention of AMPK from causing adipocyte differentiation is given the **Figure 5**.

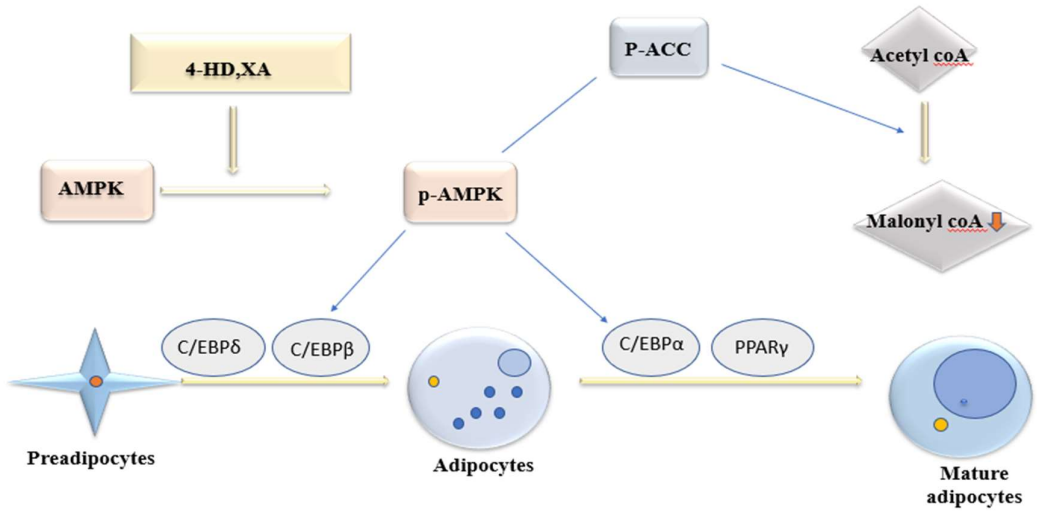

Figure 5: Illustrates the theory of how 4-HD and XA prevent AMPK from causing adipocyte differentiation

Ohta *et al*. examined the 1.47- or 1.48-fold glucose absorption by 3T3-L1 adipocytes or L6 myotubes after 10 mM 4-HD/XA stimulation with unstimulated cells. The main mechanism was shown to be the activation of AMPK's phosphorylation, which results in upstream of AMPK and downstream targets Acetyl-CoA carboxylase and liver kinase B1 (LKB1). Using SiRNA to downregulate LKB1 expression, it was discovered that 4-HD and XA-induced Glut4-dependent glucose absorption via the LKB1/AMPK signalling pathway in 3L3-L1 adipocytes could be attenuated **[26]**. Effect of Ashitaba prenylated chalcones on Glut 4 translocation is shown in **Figure 6**.

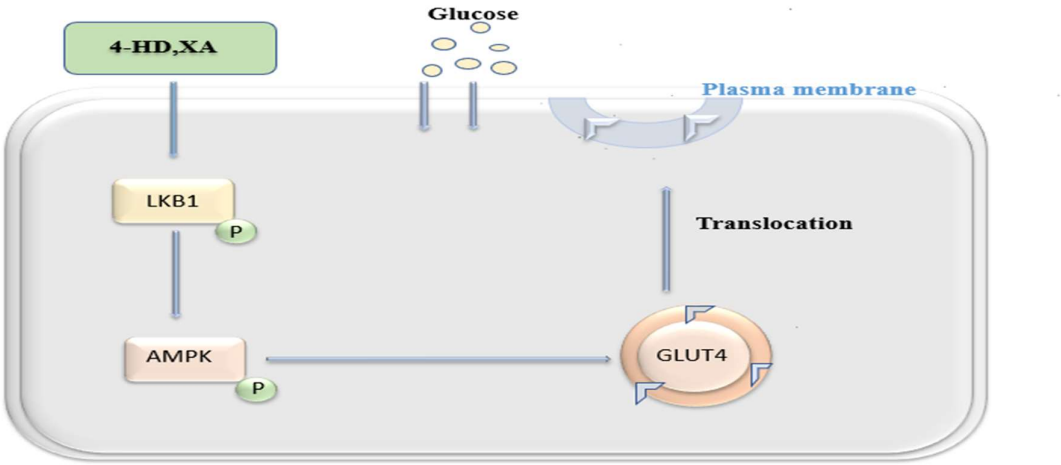

Figure 6: Effect of Ashitaba prenylated chalcones on Glut 4 translocation

c) 2-Deoxy Glucose uptake in rat L6 muscle cells

Kawabata *et al*. looked at the critical part that prenylated chalcones, which are prevalent in ACP and include 4-HD and XA, play in increasing 2-Deoxy Glucose uptake by 1.9-fold at 10 M in rat L6 muscle cells when compared to the level in DMSO-treated control cells. By increasing Glut-4 translocation and causing skeletal muscle-associated glucose uptake into the plasma membrane of L6 cells via induction of protein kinase C, Akt, or adenosine monophosphate-activated protein kinase inhibition, oral administration of ashitaba extract containing a dose of 150.6 mg/g of 4-HD and 146 mg/g of XA (dry base) has suppressed acute hyperglycemia **[27]**.

d) Inhibitory effect of α-glucosidase by XA

The inhibitory impact of XA's α-glucosidase was demonstrated by Luo *et al*. at an IC50 value of 20μm for the substrate 4-nitrophenyl -D-glucopyranoside, a value that is lower than that of the control medication acarbose at 384μm. This crucial enzyme, known as α-glucosidase, may be found in the small intestine's brush boundary where it converts carbohydrates to glucose. By blocking the target enzyme α-glucosidase and reducing the digestion of carbohydrates, this demonstrated the suppressing effect of the beginning of hyperglycemia **[28]**.

e) Inhibitory effects of chalcone extract on protein tyrosine phosphatase 1B (PTP1B)

Using oleanolic acid as a positive control, Li *et al* assessed the inhibitory effects of chalcone extract on protein tyrosine phosphatase 1B (PTP1B) in A. keiskei with IC50 values of 0.82 g/mL. PTP1B has been recommended as a very potential therapeutic target for type 2 diabetes because it downregulates insulin signalling **[22]**.

f) Increased gene expression due to ethanolic extract of ACP

Male Wistar rats were given an ethanolic extract of A. keiskei to consume for around 11 weeks along with water that contained 15% fructose, and this drastically decreased their blood sugar and serum insulin levels. The primary pathogenic theory underlying this may be the increased expression of the genes for apolipoprotein A1 (APOA1), ATP-binding membrane cassette transporter A1, medium-chain acyl CoA dehydrogenase (AMCAD), and acyl-CoA oxidase 1 (ACOX1) **[29]**.

g) Hypoglycemic effect of ACP in male diabetic KK-Ay mice

In a 4-week trial using 5-week male genetically diabetic KK-Ay mice fed a basal diet containing 0.15% of each chalcone (4-HD/XA) ad libitum, blood glucose levels were measured in each animal, and the effect of 4-HD)/XA in

suppressing acute hyperglycemia was confirmed. Blood glucose levels were discovered to be decreased by XA by 33% and 4-HD by roughly 50%. Then, by comparing the data with those from the same animal model fed with 0.05% pioglitazone, one of the PPAR-agonists prescribed to treat and improve insulin resistance in NIDDM patients, the effects of 4-HD consumption for 7 weeks on hyperglycemia, polydipsia, and body weight were assessed. No negative effects were noticed. The findings showed that 4-HD reduces polydipsia, hyperglycemia, and weight gain, likely as a result of reducing insulin resistance **[30]**.

9.3 CLINICAL STUDY

Adiponectin upregulation by ACP

Blood glucose levels were decreased by raising adiponectin in human individuals with borderline or mild hyperglycemia after 12 weeks of consuming *Angelica keiskei* powder. Adiponectin reduces insulin resistance, hence drugs that boost adiponectin synthesis may be effective in preventing the onset of metabolic syndrome conditions like diabetes. Adiponectin mRNA expression was shown to be upregulated by all chalcones, it was discovered **[31]**.

CONCLUSION

According to the review, prenylated chalcones, which are abundant in ACP, support a hypoglycemic potential by boosting the Nrf2-ARE-Keap1 signalling pathway, which in turn prevents the oxidative damage that is brought on by high blood sugar levels. Overall, the evidence from this analysis points to ACP as a promising therapy option for hyperglycemia.

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