The Inhibitory Potential of Natural Compounds on α-Amylase and α-Glucosidase in the Management of Type 2 Diabetes

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ABSTRACT: *In an effort to find effective medicines for the treatment of diabetes, the efficient mechanisms and lack of side effects of herbal medicines have made them the main candidates for regulating blood sugar levels and reducing the side effects of the disease. This search will be based on the discovery of digestive enzymes (α-amylase and α-glucosidase) inhibitors from natural sources and the ways to reduce high blood sugar levels. These enzymes are at the forefront of increasing blood glucose levels because they facilitate the digestion of food polysaccharides into smaller monosaccharide in small intestinal wall. Currently, the arsenal of inhibitors approved for this purpose is limited to veglibose, miglitol and acarbose. Despite the ability to reduce glucose absorption their widespread clinical use is limited due to the occurrence of gastrointestinal ailments. Given the efficacy of various natural compounds in alleviating diabetes symptoms, this review aims to assess the inhibitory potential and mode of action of some phytochemicals on intestinal digestive enzymes. Such an exploration seeks to unveil novel and healthful anti-diabetic agents based on the inhibition of digestive enzymes.*

KEYWORDS: *Diabetes mellitus, Polyphenols, Biological activity, Anti-diabetic potential.*

INTRODUCTION

Today, due to the expensive treatment of diabetes and also the contraindications of these drugs, many people are willing to discover the wonders of alternative herbal remedies for diabetes [1-3]. Some argue that natural ingredients are not harmful to health unless consumed in large amounts. Any drug, herbal or chemical, should always be used in moderation. According to ethnobotanical data, about 800 plants may have antidiabetic potential [4-6]. Most herbal medicines focus on lowering blood sugar levels and reducing the side effects of diabetes. Recently, we have

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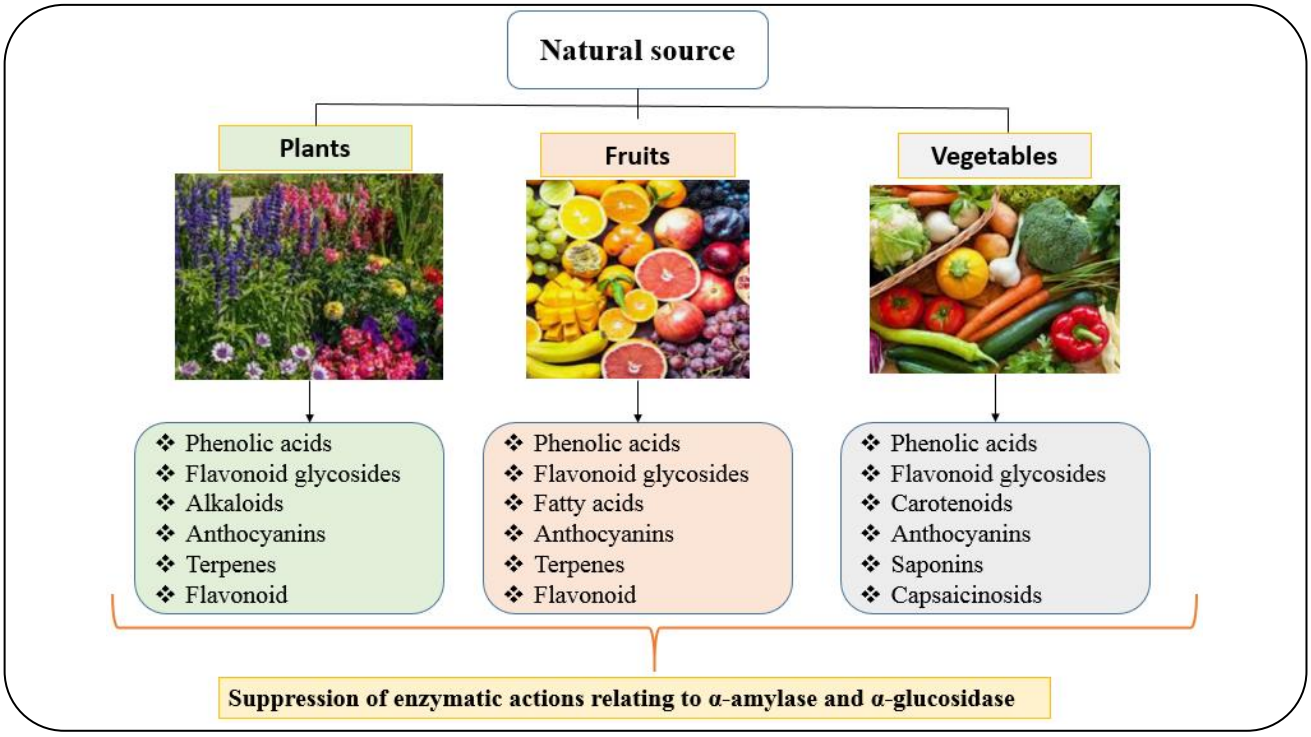


Fig. 1: Naturally occurring phytochemicals, vegetables and fruits are classified based on inhibition capacity against digestive enzymes, α-amylase and α-glucosidase; Phytochemicals, which are natural compounds found abundantly in plants, vegetables, and fruits, have been classified systematically because of their unique ability to slow down the activities of important digestive enzymes like α-amylase and α-glucosidase. These bioactive compounds, including polyphenols, flavonoids, alkaloids, and terpenoids, have different inhibitory effects on these enzymes. The classification is based on their strength and the ways they regulate the breakdown of complex carbohydrates into simpler sugars, impacting the body's response to sugar levels. This classification helps us understand and utilize these natural compounds for various health purposes, especially in managing and controlling blood sugar levels and related metabolic processes.

investigated several plant compounds in our laboratory under in vitro and in vivo conditions [7,8].

In this regard, among the organs, the small intestine and its digestive enzymes are the target of herbal treatments. Treatment based on this approach is mainly through the control of circulating glucose levels (glucose production, consumption, consumption). The intended strategy is based on reducing the effects of blood sugar through the inhibition of digestive enzymes, α-amylase and α-glucosidase, which digest carbohydrates into smaller monosaccharide pieces and are easily absorbed through the walls of the small intestine [9-11]. Common inhibitors of digestive enzymes are voglibose, acarbose and miglitol [12,13]. However, the occurrence of adverse gastrointestinal side effects caused by these drugs necessitates the investigation of new approaches. Plant-derived inhibitors can be an alternative strategy in the development of anti-diabetic natural products. Accordingly, more research is needed to determine to what extent polyphenols and other plant compounds have beneficial health effects through inhibition of carbohydrate catabolizing enzymes, or their antioxidant activity in quenching ROS [14-16].

Throughout history, the natural world has been a rich source of many different active compounds. These compounds have shown various health benefits, which are important for human well-being [17, 18]. An abundance of empirical research has established beyond doubt that vegetables and fruits constitute a rich reservoir of secondary metabolites filled with notable α-amylase and α-glucosidase inhibition activities, comprising an extensive array of bioactive compounds such as alkaloids [19], flavonoid glycosides, fatty acids [20], capsaicinoids [21], terpenes [22,23], proteins [24], carotenoids [25], saponins [26], phenolic acids [27], Coumarins [28], and anthocyanins [29] (Fig. 1). Consequently, the utilization of fruits and vegetables as viable sources for the development of natural supplements presents an intriguing possibility for the creation of effective alternatives to conventional pharmaceuticals.

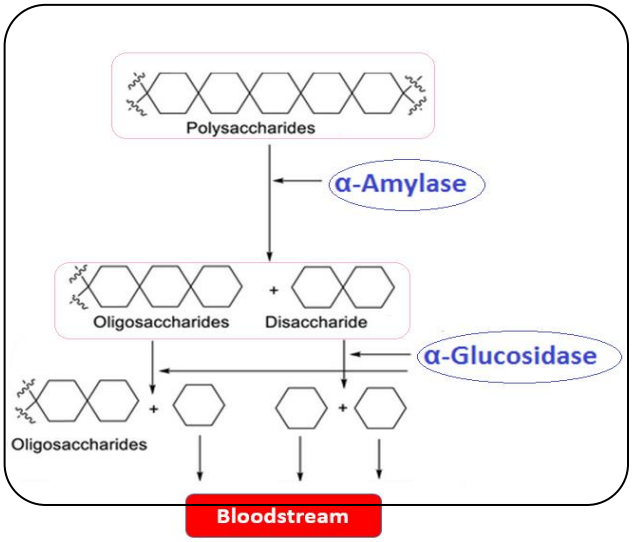


Fig. 2: Enzymatic process of starch hydrolysis involves sequential biochemical reactions facilitated by the synergistic action of α-amylase and α-glucosides. Breaking down of starch into shorter polysaccharide chains catalysed by α-amylase, which finally converted to individual glucose units by the action of α-glucosidase.

pharmaceuticals. Anyway, this review focuses on diabetes treatment based on α-glucosidase and α-amylase inhibition by natural compounds.

FUNCTIONAL SIGNIFICANCE OF α-AMYLASE AND α-GLUCOSIDASE ENZYMATIC ACTIVITIES IN BIOLOGICAL SYSTEMS

The investigation of the biochemical pathways and enzymatic activities involved in the hydrolysis of complex carbohydrates, notably starches, has been a longstanding area of scientific inquiry [9]. One central focus of this research has been on the roles played by the α-glucosidase and α-amylase in the process of carbohydrate digestion, which is an essential component of human metabolism (Fig. 2). α-amylase is a glycoside hydrolase enzyme that acts on the α-1,4-glycosidic bonds found within the interior of starch molecules, cleaving them into smaller oligosaccharides, primarily maltose and maltotriose [30]. The efficiency of α-amylase activity is influenced by various factors, including pH levels, temperature, and the presence of specific inhibitors or activators. This enzyme is secreted in the salivary glands and pancreas and plays an essential role in the initial stages of carbohydrate digestion in the oral cavity and small intestine. α-glucosidase, also known as maltase, is another enzyme involved in the breakdown of complex carbohydrates. It acts on the α-1,4-glycosidic linkages found at the non-reducing ends of oligosaccharides, releasing glucose molecules from molecules such as maltose, maltotriose, and dextrin [31]. Located in the brush border membrane of enterocytes lining the small intestine, α-glucosidase plays a vital role in the final stages of carbohydrate digestion, facilitating the absorption of glucose into the bloodstream for use by the body's cells. The precise interactions and interplay between these two key enzymes are critical to the efficient conversion of complex carbohydrates into usable forms of energy. Understanding the mechanisms and regulation of α-glucosidase and α-amylase activity has important implications for nutrition, health, and disease management [32].

COMPOUNDS THAT INHIBIT CARBOHYDRATE-DIGESTING ENZYMES

Alkaloids

Alkaloids are a diverse group of natural compounds that have been studied for their therapeutic potential. They've gained attention for their natural anti-diabetic properties and their ability to inhibit digestive enzymes [33]. The inhibition mechanism depends on factors like chemical structure, enzyme affinity, and the inhibition type. Most alkaloids bind to the active site of digestive enzymes, disrupting their catalytic activity and suppressing the breakdown of complex carbohydrates into simpler sugars [34]. Some alkaloids known for inhibiting α-amylase and α-glucosidase enzymes include (Fig. 3A-C): (a) Australine, which has a unique molecular structure that inhibits the activity of these enzymes, interfering with the breakdown of complex carbohydrates and affecting glucose release. (b) Casuarine, with a distinctive structural layout aimed at inhibiting the catalytic action of α-amylase and α-glucosidase, contributing to its efficacy as an enzyme inhibitor. (c) Hyacinthacine, recognized for its inhibitory effects on α-amylase and α-glucosidase, strategically interacting with these enzymes and impeding their functions in carbohydrate breakdown and glucose release. These alkaloids, found in the bark of *Casuarina equisetifolia* and the leaves of *Eugenia jambolana*, are crucial in developing compounds to regulate carbohydrate metabolism and manage glycemic responses. Recent synthesis methods have allowed the creation of these alkaloids in a single procedural step. The potency of alkaloids

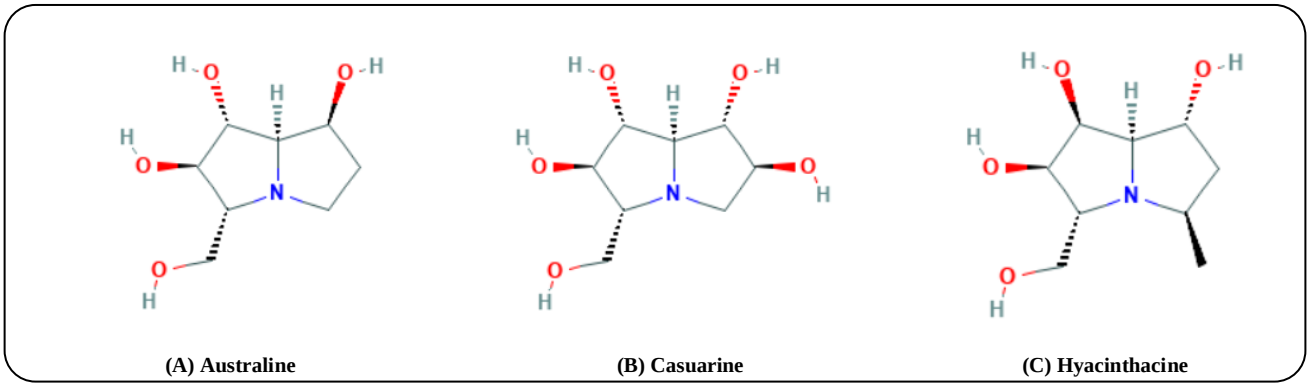


Fig. 3: Structure of some of the described alkaloids as α-amylase and α-glucosidase inhibitors; (A) Australine, (B) Casuarine, and (C) Hyacinthacine.

as inhibitors varies based on their chemical structure and functional groups [35]. Further research is warranted to fully elucidate the molecular mechanisms underlying the inhibitory effects of alkaloids on these enzymes, facilitating the development of novel therapeutic strategies for metabolic disorders.

Flavonoid glycosides

Flavonoid glycosides are a class of naturally occurring compounds that have been extensively studied for their ability to modulate various biological processes, including carbohydrate metabolism. In particular, the inhibitory effects of flavonoid glycosides on α-amylase and α-glucosidase have garnered significant attention due to their potential therapeutic implications [36]. Flavonoid glycosides exert their inhibitory effects on α-amylase and α-glucosidase through various mechanisms, including binding to the active site of these enzymes, thereby impeding their catalytic activity. The potency of flavonoid glycosides as inhibitors depends on several factors, including the number and position of the hydroxyl groups, the nature of the sugar moiety, and the conjugation pattern of the flavonoid aglycone [37]. Additionally, the mode of inhibition exhibited by these compounds varies depending on the specific enzyme targeted, with some flavonoid glycosides acting as competitive inhibitors. The potential of flavonoid glycosides as natural antidiabetic agents has been demonstrated through various in vitro and in vivo studies. Consumption of flavonoid glycoside-rich diets has been shown to reduce blood glucose levels and improve insulin sensitivity in animal models, providing evidence for their therapeutic potential [38, 39]. Further research is warranted to fully elucidate the molecular mechanisms underlying the inhibitory effects of flavonoid glycosides on these enzymes, paving the way for the development of novel therapeutic agents for metabolic disorders.

Fatty acids

Fatty acids are crucial for lipid metabolism, providing energy and contributing to cell membrane structure. Recent research has uncovered their potential role in controlling carbohydrate metabolism by inhibiting digestive enzymes [40]. Fatty acids hinder these enzymes through various means, such as binding to the active site and disrupting their catalytic activity. The effectiveness of fatty acids as inhibitors depends on factors like chain length, degree of unsaturation, and the presence of functional groups [41]. For instance, long-chain saturated fatty acids show stronger inhibitory effects compared to shorter chain fatty acids. Studies, both *in vitro* and *in vivo*, have validated the potential of fatty acids as natural anti-diabetic agents. Adding specific fatty acids to the diet has been found to lower blood glucose levels and enhance insulin sensitivity in animal models [20]. These findings suggest that fatty acids could be a promising therapeutic option for managing high blood sugar and related metabolic issues. To fully understand how fatty acids inhibit digestive enzymes, more research is needed. This exploration could lead to the development of innovative therapeutic agents for metabolic disorders.

Capsaicinoids

Capsaicinoids are a class of bioactive compounds found in chili peppers that have gained increasing attention for their potential health benefits. Among these benefits is the modulation of carbohydrate metabolism through

the inhibition of α-glucosidase and α-amylase [21]. Capsaicinoids exert their inhibitory effects on α-glucosidase and α-amylase through various mechanisms, including binding to the active site of the enzyme and interfering with its catalytic activity. The potency of capsaicinoids as inhibitors depends on several factors, including the number and position of hydroxyl groups and the presence of a vanillyl moiety [42]. *In vitro* and *in vivo* studies have confirmed the potential of capsaicinoids as natural antidiabetic agents. Consumption of capsaicinoid-rich diets has been shown to lower blood glucose levels and improve insulin sensitivity in animal models, providing evidence for their therapeutic potential. Furthermore, capsaicinoids have been demonstrated to possess anti-obesity properties, further highlighting their potential applications as natural therapeutics for metabolic disorders [43]. To fully understand how capsaicinoids inhibit α-glucosidase and α-amylase, more research is needed. This exploration could lead to the development of innovative therapeutic agents for metabolic disorders.

Terpenes

Terpenes, a diverse group of natural compounds found abundantly in plants, have been attracting attention due to their therapeutic potential. One of their notable biological activities is their ability to influence carbohydrate metabolism by inhibiting α-glucosidase and α-amylase [22]. Terpenes exert their inhibitory effects on α-glucosidase and α-amylase through various mechanisms, including binding to the active site of the enzyme and interfering with its catalytic activity. The potency of terpenes as inhibitors depends on several factors, including the chemical structure of the compound, its lipophilicity, and hydrophobicity. For example, monoterpenes containing a carbonyl group have been shown to exhibit stronger inhibitory effects than those lacking this functional group. In vitro and in vivo studies have confirmed the potential of terpenes as natural antidiabetic agents. The chemical structures of select terpenoids recognized for their role as inhibitors of α-glucosidase and α-amylase are outlined below:

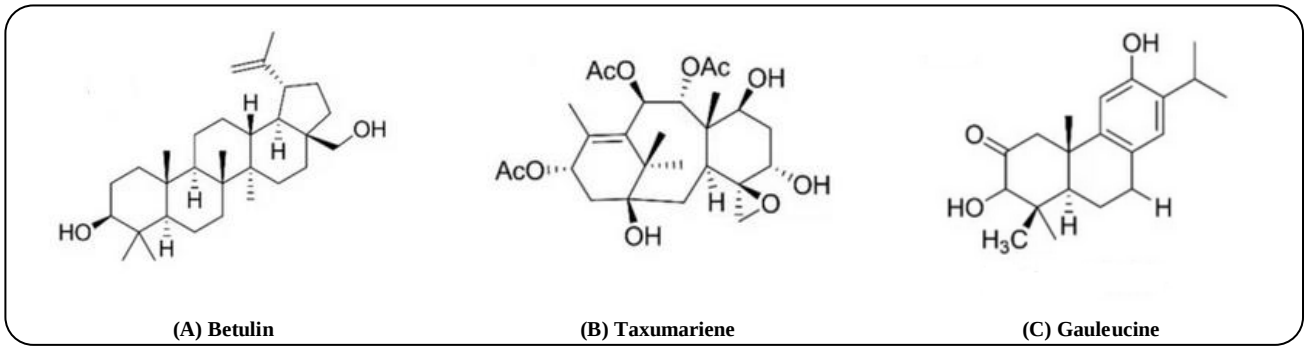
(a) Betulin: with its unique molecular arrangement, betulin stands as a prominent terpenoid compound identified for its potent inhibitory effects on α-glucosidase and α-amylase. Its specific structural composition facilitates a robust interference with the enzymatic breakdown of complex carbohydrates, influencing the regulation of glucose release within biological systems.

(b) Taxumariene: this terpenoid displays a distinct chemical structure, tailored to inhibit the catalytic activity of α-amylase and α-glucosidase. Its molecular framework encompasses functional groups crucial for impeding the enzymatic processes involved in breaking down starch into simpler sugars, thereby affecting glucose metabolism.

(c) Gauleucine: notable for its molecular configuration, gauleucine demonstrates inhibitory effects on α-amylase and α-glucosidase. Its specific structural features are strategically positioned to interact with these enzymes, disrupting their catalytic functions in carbohydrate breakdown and subsequent glucose release.

These terpenoids, characterized by their intricate and diverse molecular architectures, serve as pivotal candidates in the exploration of compounds designed to regulate carbohydrate metabolism and modulate glycemic responses within biological systems.

Three abietane-type diterpenoids betulin, taxumariene, and Gauleucine originating from *Gaultheria leucocarpa* were identified (Fig. 4A-C). *Chen* and colleagues detailed seven novel taxane diterpenoids, including taxumariene from *Taxus mairei*, while investigating their inhibitory effects on α-amylase and α-glucosidase. *Yuca et al*. conducted an assessment on the antidiabetic properties of triterpenes isolated from *Paliurus spina* mill fruit. Notably, betulin demonstrated a substantial inhibition of α-glucosidase, surpassing acarbose by 17-fold with an IC_{50} of 232 ± 14 μM. These results prompt further exploration into potential synergistic and antagonistic interactions among diverse terpenoid compounds concerning their inhibitory action on α-amylase and α-glucosidase. Therefore, comprehensive investigations, including kinetics studies and structure-activity relationship analyses, are imperative for a deeper understanding of the mechanisms underlying the differential inhibitory effects of various terpenoid molecules on α-amylase and α-glucosidase [44]. Consumption of terpene-rich diets has been shown to lower blood glucose levels and improve insulin sensitivity in animal models, providing evidence for their therapeutic potential. Further research is necessary to fully elucidate the molecular mechanisms underlying the inhibitory effects of terpenes on α-amylase and α-glucosidase, paving the way for the development of novel therapeutic agents for metabolic disorders. Overall, the growing body of evidence



(A) Betulin **(B) Taxumariene** **(C) Gauleucine**

Fig. 4: Chemical structure of some of the described terpenoids as α-amylase and α-glucosidase inhibitors; (A) Betulin, (B) Taxumariene, and (C) Gauleucine.

highlights the potential of terpenes as natural antidiabetic agents, offering new avenues for the development of effective treatments for metabolic disorders [45].

Proteins

Proteins are fundamental biomolecules that play various essential roles in biological processes, including the regulation of carbohydrate metabolism. Recent research has focused on the inhibitory effects of specific proteins on digestive enzymes, offering new insights into novel therapeutic targets for metabolic disorders [24]. Proteins exert their inhibitory effects on α-amylase and α-glucosidase through various mechanisms, including binding to the active site of the enzyme and interfering with its catalytic activity. The potency of proteins as inhibitors depends on several factors, including the protein's molecular weight, charge, and the presence of functional groups that facilitate binding to the enzyme. For example, some plant-derived proteins containing lectin domains have been shown to exhibit potent inhibition of α-amylase and α-glucosidase [46]. *In vitro* and *in vivo* studies have confirmed the potential of proteins as natural antidiabetic agents. Consumption of protein-rich diets has been shown to lower blood glucose levels and improve insulin sensitivity in animal models, providing evidence for their therapeutic potential. Further research is necessary to fully elucidate the molecular mechanisms underlying the inhibitory effects of proteins on α-amylase and α-glucosidase, paving the way for the development of novel therapeutic agents for metabolic disorders [47]. These findings underscore the importance of continued research efforts aimed at elucidating the role of proteins in regulating carbohydrate metabolism and identifying new targets for therapeutic intervention.

Carotenoids

The investigation of compounds with inhibitory effects on digestive enzymes represents an important area of research in the field of nutritional and pharmaceutical sciences. Carotenoids, a class of lipophilic pigments widely distributed in nature, have been shown to possess antidiabetic properties primarily attributed to their ability to modulate glucose metabolism [25]. Carotenoids have been found to interact with these enzymes through various mechanisms, such as competitive or non-competitive inhibition or modulation of enzyme kinetics. The molecular structure of carotenoids appears to play a critical role in determining their inhibitory potential, with some specific analogues exhibiting stronger inhibitory effects than others [48]. Furthermore, the bioavailability and absorption of carotenoids may also impact their inhibitory activity, with intact carotenoids showing better efficacy compared to their metabolites. Overall, the available literature highlights the potential of carotenoids as a promising source of natural compounds for the development of novel therapeutic agents targeting α-amylase and α-glucosidase inhibition [49]. Further investigation is required to fully understand the underlying mechanisms and to optimize the use of carotenoids for the management of hyperglycemia and associated metabolic disorders.

Saponins

The potential use of plant-derived compounds for the management of hyperglycemia and related metabolic disorders has gained significant interest in recent years. Among these, saponins represent a class of naturally occurring glycosides that have been investigated for their ability to inhibit α-amylase and α-glucosidase [26]. The inhibitory effect of saponins on these enzymes has been

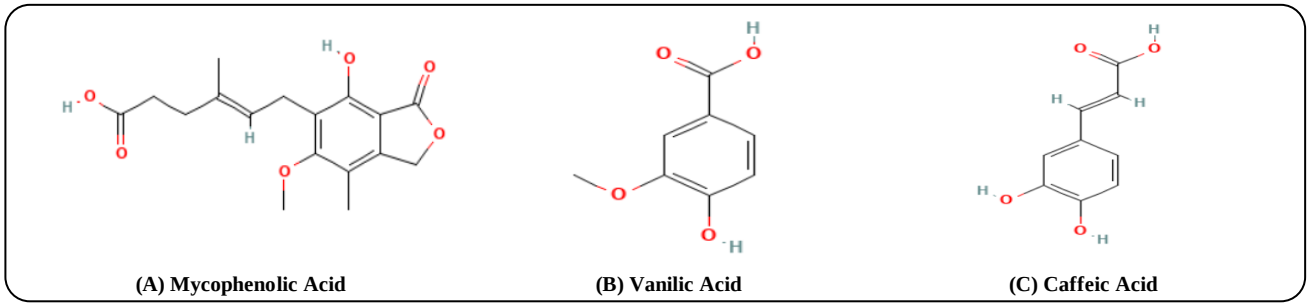


Fig. 5: Structure of some of the described phenolic acids as α-amylase and α-glucosidase inhibitors; (A) mycophenolic acid, (B) vanilic acid, and (C) caffeic acid.

attributed to their structural features, including the presence of hydrophobic triterpene or steroid aglycone moiety and one or more sugar chains [50]. These structural features enable saponins to form complexes with enzymes, thereby inhibiting their activity. Furthermore, the type and arrangement of sugar chains in saponins appear to influence their inhibitory potency, with some saponins showing higher activity than others. In addition to their inhibitory effects on α-amylase and α-glucosidase, saponins have been reported to exhibit other beneficial properties relevant to diabetes management, including insulin sensitization, glucose uptake promotion, and pancreatic β-cell protection [51]. These properties are thought to be mediated through various signaling pathways, such as and Peroxisome Proliferator-Activated Receptors (PPARs) and AMP-activated protein kinase (AMPK). Overall, the available literature suggests that saponins represent a promising avenue for the development of novel therapeutic agents for the management of hyperglycemia and related metabolic disorders. However, further research is required to fully understand the underlying mechanisms of their action and optimize their efficacy and safety profile.

Phenolic acids

Phenolic acids are a group of natural compounds that have been studied for their potential to inhibit α-glucosidase and α-amylase [27]. Phenolic acids exhibit inhibitory effects on α-amylase and α-glucosidase enzymes through various mechanisms, including competitive and non-competitive inhibition, as well as modulation of enzyme kinetics [52]. These inhibitory effects have been attributed to the structural features of phenolic acids, including the presence of hydroxyl groups and carboxylic acid moieties, which enable them to interact with target enzymes and disrupt their activity [53]. The degree and position of these functional groups appear to affect the potency of phenolic acids as inhibitors of α-glucosidase and α-amylase. In addition to their inhibitory effects on these enzymes, phenolic acids exhibit other beneficial properties relevant to diabetes management, such as antioxidant, anti-inflammatory, and insulin sensitizing activities [54]. These properties are thought to be mediated through various signaling pathways, including the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway, Mitogen-Activated Protein Kinase (MAPK) pathway, and peroxisome proliferator-activated receptors (PPARs). Mycophenolic Acid, extracted from *Eugenia jambolana*, demonstrates robust α-amylase inhibitory characteristics with an IC_{50} of 3.0 ± 0.57µM, marking an 11-fold increase compared to the positive control. *Aleixandre et al*. delved into the interactions of vanilic acid and caffeic acid with α-glucosidase or the substrate, employing varied conditions, including preincubation of phenolic acids with the enzyme or substrate and starch gelation in their presence (Fig. 5A-C). Vanilic acid and caffeic acid exhibit notable α-amylase inhibition activity, displaying IC_{50} values of 99.7 and 67.8 µM, respectively, markedly lower than acarbose (IC_{50} = 1200 µM). These promising outcomes designate them as potential candidates for lead optimization. Nonetheless, further investigation is essential to evaluate their potential toxicity. Overall, the available literature suggests that phenolic acids represent a promising class of natural compounds for the development of novel therapeutic agents targeting α-glucosidase and α-amylase inhibition [55].

Anthocyanins

Anthocyanins are a class of flavonoids widely distributed in fruits and vegetables, which have attracted

considerable attention for their potential health benefits. Recent studies have shown that anthocyanins possess inhibitory effects on α-glucosidase and α-amylase [29]. Anthocyanins exhibit inhibitory effects on α-glucosidase and α-amylase through various mechanisms, including competitive and non-competitive inhibition, as well as modulation of enzyme kinetics [56]. These inhibitory effects have been attributed to the structural features of anthocyanins, including the presence of hydroxyl groups and sugar moieties, which enable them to interact with target enzymes and disrupt their activity. The degree and position of these functional groups appear to affect the potency of anthocyanins as inhibitors of α-glucosidase and α-amylase. In addition to their inhibitory effects on these enzymes, anthocyanins exhibit other beneficial properties relevant to diabetes management, such as antioxidant, anti-inflammatory, and insulin sensitizing activities [57]. These properties are thought to be mediated through various signaling pathways (Nrf2 pathway, MAPK pathway, and PPARs) [58]. Additionally, the bioavailability and metabolism of anthocyanins may impact their overall health benefits, warranting further investigation.

Flavonoids

Polyphenolic compounds such as flavonoids have been extensively studied for their ability to modulate various biological processes. In particular, the inhibitory effects of flavonoids on α-glucosidase and α-amylase have garnered significant attention owing to their potential therapeutic implications [59]. Flavonoids possess the ability to bind these enzymes, thereby inhibiting their catalytic activity. Various structural features such as the number and position of hydroxyl groups, conjugation pattern, and glycosylation status influence the potency of flavonoids as inhibitors [39]. Additionally, the mode of inhibition exhibited by these compounds varies depending on the specific enzyme targeted. While some flavonoids act as competitive inhibitors, others exhibit non-competitive or mixed inhibition [36]. The significance of flavonoids as potent inhibitors of on α-glucosidase and α-amylase has been demonstrated in both *in vitro* and *in vivo* studies. Consumption of flavonoid-rich diets has been shown to lower blood glucose levels and improve insulin sensitivity in animal models, providing evidence for their potential as natural therapeutics for managing hyperglycemia [60].

Coumarins

Coumarins have emerged as a class of molecules that exhibit a wide range of biological activities including anti-inflammatory, anticancer, antioxidant, antimicrobial and antiviral properties [61]. One of the most notable biological activities associated with coumarins is their ability to inhibit the activity of α-glucosidase and α-amylase [62]. The inhibitory effects of coumarins on digestive enzymes can be attributed to their structural features which enable them to interact with the active sites of these enzymes and interfere with their catalytic mechanisms. Coumarins possess a planar structure with a fused benzene ring and a lactone moiety which provide them with the necessary chemical properties to form strong hydrogen bonds, hydrophobic interactions, and *pi-pi* stacking interactions with the amino acid residues present in the active sites of these enzymes. Furthermore, the presence of functional groups such as hydroxyl, methoxyl and acetyl groups on the coumarin skeleton, contributes to their inhibitory potency by enhancing their binding affinity towards the active site of the target enzymes [63].

INVESTIGATION OF THE VARIETIES OF CRUD EXTRACTS ON DIGESTIVE ENZYMES

Plant extracts

Plant-based extracts are known to exhibit a diverse range of biological activities that have potential therapeutic applications. In particular, crude plant extracts have emerged as a promising source of natural compounds with inhibitory effects on α-glucosidase and α-amylase [64]. Crude plant extracts contain a complex mixture of secondary metabolites including alkaloids, flavonoids, phenolics, terpenoids, and saponins, among others [65]. These molecules possess diverse structural features that enable them to interact with the α-amylase and α-glucosidase and inhibit their activity. The precise mechanism by which these natural compounds interact with the target enzymes, is not yet fully understood, but it is believed to involve a combination of non-covalent interactions such as hydrogen bonding, hydrophobic interactions, and *pi-pi* stacking interactions. The inhibitory effects of crude plant extracts on these enzymes have been attributed to the presence of various classes of natural compounds within the extract [55]. For instance, alkaloids such as berberine and sanguinarine, present in plants like *Berberis aristata* and *Macleaya cordata*, respectively,

have been shown to inhibit α-amylase and α-glucosidase. Similarly, flavonoids and phenolics such as quercetin and resveratrol, present in plants like *Allium cepa* and *Vitis vinifera*, respectively, have also been reported to possess inhibitory effects on these enzymes [66]. Furthermore, the synergistic effects of the different bioactive components within crude plant extracts could contribute to their potent inhibitory activities. Mixtures of different natural compounds may enhance their binding affinity towards the target enzymes, providing a more effective inhibition of enzyme activity than single compounds alone. In conclusion, the demonstrated inhibitory effects of crude plant extracts on α-amylase and α-glucosidase suggest their potential as a source of natural compounds with therapeutic effects in managing conditions such as hyperglycemia and diabetes [67].

Fruit extracts

In recent years, crude fruit extracts have emerged as potential sources of bioactive compounds that can impede the catalytic activity of these enzymes [68]. The biological activities of natural products have been extensively studied, and crude fruit extracts have shown promise due to their diverse array of bioactive compounds like flavonoids, phenolic compounds, tannins, and others that exhibit inhibitory effects on α-glucosidase and α-amylase. The active sites of these enzymes are targeted by the aforementioned compounds present in crude fruit extracts (such as *Prunus avium*, *Prunus cerasus*) which results in the disruption of their normal catalytic activities [69]. Apart from this mechanism, crude fruit extracts also exhibit other modes of action that help in managing hyperglycemia, such as reducing postprandial blood glucose levels by hampering glucose absorption in the small intestine and improving insulin sensitivity in animal models. There is a need for further studies to identify specific bioactive compounds present in crude fruit extracts and understand their mechanisms of action so that they can be used as therapeutic agents for the management of metabolic disorders [58]. Additionally, the safety and toxicity profiles of these compounds need to be determined to ensure optimal dosage regimens for clinical applications.

Vegetable extracts

Among these natural compounds, vegetable extracts have shown promising inhibitory activity against digestive enzymes [70-71]. Vegetable extracts contain various phytochemicals, including polyphenols, flavonoids, terpenoids, and others, that have been found to possess potent inhibitory effects on α-glucosidase and α-amylase. The bioactive compounds present in vegetable extracts act by binding to the active sites of these enzymes and thereby impeding their normal catalytic activity, leading to a reduction in the rate of carbohydrate digestion and absorption [72-73]. Additionally, these compounds may also exhibit other mechanisms of action, such as reducing postprandial blood glucose levels by inhibiting glucose absorption in the small intestine and increasing insulin sensitivity in animal models. Despite the promising results obtained from studies investigating the role of vegetable extracts in inhibiting α-glucosidase and α-amylase, there is still a need for further research to identify specific bioactive compounds responsible for this activity and to elucidate their mechanisms of action. Furthermore, investigations into the safety, efficacy, and optimal dosage regimens of these compounds must be conducted before they can be considered for clinical applications [74]. The discovery and characterization of these compounds could lead to the development of novel therapeutic agents for the treatment and prevention of metabolic disorders.

CONCLUSIONS

α-amylase and α-glucosidase, fundamental enzymes in the intricate process of dietary carbohydrate catabolism, hold pivotal roles in regulating postprandial glucose levels and overall insulin sensitivity. The inhibition of these enzymes has emerged as promising strategy by reducing the rapid influx of glucose, not only aids in managing immediate postprandial glucose peaks but also contributes to long term insulin sensitivity. The resulting control of glucose levels post-meal consumption offers a pathway for potential pharmacological interventions aimed at managing glycemic control, making these enzymes highly attractive targets for therapeutic strategies and pharmaceutical development. This review introduced some herbal compounds with strong alpha-amylase and α-glucosidase inhibitory properties, including alkaloids, flavonoids, phenolic acids and terpenoids. It has been found that these compounds interact with these enzymes through reversible mechanisms and after inhibiting them, they can effectively reduce blood glucose levels in animal and human models. These studies point to the inhibitory

potential of such compounds as a safe and effective treatment platform for type 2 diabetes.

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