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REVIEW ARTICLE

Nutritional and medicinal plants as potential sources of enzyme inhibitors toward the bioactive functional foods: an updated review

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ABSTRACT

Enzymes are biologically active complex protein molecules that catalyze most chemical reactions in living organisms, and their inhibitors accelerate biological processes. This review emphasizes medicinal food plants and their isolated chemicals inhibiting clinically important enzymes in common diseases. A mechanistic overview was investigated to explain the mechanism of these food bases enzyme inhibitors. The enzyme inhibition potential of medicinal food plants and their isolated substances was searched in Ovid, PubMed, Science Direct, Scopus, and Google Scholar. Cholinesterase, amylase, glucosidase, xanthine oxidase, tyrosinase, urease, lipoxygenase, and others were inhibited by crude extracts, solvent fractions, or isolated pure chemicals from medicinal food plants. Several natural compounds have shown tyrosinase inhibition potential, including quercetin, glabridin, phloretin-4-O-β-D-glucopyranoside, lupinalbin, and others. Some of these compounds' inhibitory kinetics and molecular mechanisms are also discussed. Phenolics and flavonoids inhibit enzyme activity best among the secondary metabolites investigated. Several studies showed flavonoids' significant antioxidant and anti-inflammatory activities, highlighting their medicinal potential. Overall, many medicinal food plants, their crude extracts/fractions, and isolated compounds have been studied, and some promising compounds depending on the enzyme have been found. Still, more studies are recommended to derive potential pharmacologically active functional foods.

KEYWORDS

Enzyme inhibition; flavonoids; functional foods; natural products; nutritional plants; phytochemicals

Introduction

Since ancient times, food and natural products have been used in different parts of the world as traditional medicine, depending on their high therapeutic efficacy in treating various diseases. To date, using natural products offers high biocompatibility with marginal side effects. Thus, they have contributed to the development of up to 50% of the approved drugs in the market (Kamarudin et al. 2017; Newman and Cragg 2016). Traditional herbal medicines have played a fundamental role in preventing and treating various ailments since ancient times, which are rich sources for new drug discovery (Shendge and Belemkar 2018). The prescribed drugs derived from higher plants have increased by 25% in the last few decades (Khaliq 2017). The WHO has declared that 11% of the 252 drugs are from plant sources, while various synthetic drugs have natural precursors (Saleem, Zengin, et al. 2019; Cvetanović et al. 2018). Especially with the worldwide spread of diseases such as diabetes mellitus (DM), cardio-metabolic, cancer, and Alzheimer's diseases (AD) are being focused on safe and consistent natural drugs over synthetic ones and side effects (Mocan et al. 2016).

Enzymes are essential to human life, mediating biochemical processes, including metabolism, cellular signal transduction, cell cycling, and development. Malfunction in these biochemical systems often leads to disease, the root cause of which can often be traced to the dysfunction, overexpression, or hyperactivation of the enzymes involved (Nakao and Fusetani 2007). A key aspect of drug discovery is the identification of small molecules with enzyme-inhibiting activities (Ata, Naz, and Elias 2011). Enzymes are biologically active complex protein molecules that catalyze most of the chemical reactions in the living organism. Mechanistically, enzyme inhibitors primarily suppress enzyme activity by forming an Enzyme-Inhibitor complex with low or no enzyme activity. Enzyme inhibitors can be divided

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into two groups based on the mechanism of action, that is, (1) irreversible inhibitors and (2) reversible inhibitors. A brief explanation of the reversible enzyme inhibition reactions has been given in Figure 1. Understanding diseases at the molecular level has led to the discovery of effective enzyme inhibitors used in clinical practice. Two such inhibitors are the cholesterol-lowering agent lovastatin (mevinolin) and the acetylcholinesterase (AChE) inhibitor galantamine. Lovastatin acts at a key step in cholesterol biosynthesis, inhibiting the enzyme (3S)-hydroxy methylglutaryl-coenzyme A (HMG-CoA) reductase and preventing catalysis of the reduction of HMG-CoA to mevalonate (Moore et al. 1985; Sutherland, Auclair, and Vederas 2001).

On the other hand, galantamine is a potent AChE inhibitor used to treat Alzheimer's disease (AD) (Yu et al. 2010). One of the most promising strategies to combat global health-related problems is to inhibit the key enzymes involved in specific disorders. For example, α-amylase and α-glucosidase inhibition for treating diabetes mellitus, cholinesterase inhibition for neurodegenerative diseases, and tyrosinase inhibition for skin problems. The major problem with the synthetic drugs presently treating these diseases is their associated side effects (Zengin, Locatelli, et al. 2016). Surprisingly, herbs, plants, and their plethora of secondary metabolites have proved to be potential inhibitors of these specific enzymes (Saleem, Zengin, et al. 2019).

A wide variety of medicinal and nutritional plant species encompass organic compounds that are capable of inhibiting the activity of enzymes. These molecules have a variety of potential uses, including those in the medical field and in the field of nutrition science. Considering the importance of medicinal plants as natural enzyme inhibitors for the drug discovery process, this review paper is an attempt to highlight the importance of medicinal plants exhibiting inhibitory enzyme activities against clinically essential enzymes. Investigations have mainly focused on cholinesterase, urease, xanthine oxidase, angiotensin I-converting enzyme, α-amylase and α-glucosidase, lipoxygenase and tyrosinase, which are linked with neurodegenerative disorders, *Helicobacter pylori* infections, hypertension, diabetes, inflammation, and skin problems, respectively. Table 1 describes several enzyme inhibitors having medical significance isolated from different plant sources, and their details are as follows. Likewise, several crude extracts and/or their fractions have also been documented for enzyme inhibition activities.

Classification of enzyme inhibitors

Cholinesterase inhibitors: neurological disorders

Neurodegenerative disorders, as a significant health alarm, are of particular concern in many countries where the elderly population faces neuronal loss and abnormal emotional changes. Alzheimer's disease (AD), a common neurological problem, is currently the leading cause of gradual and irreversible impairment of the brain (Parihar and Hemnani 2004). There is an extravagant boost in the prevalence of Alzheimer's disease, which is a burning challenge for public health. Likewise, according to recent reports, Alzheimer's disease has affected more than 50 million populations, and by 2050, this statistic is presumed to be increased by about three times more (Prince, 2015). Associated with aging, AD is responsible for damaging parts of the brain, including the parietal and temporal lobe and cortex. It affects the cholinergic neurons and stops acetylcholine, acetylcholinesterase (AChE) and neurotransmitter transmission (Querfurth and LaFerla 2010; Ritter 2012). Acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) are the key enzymes in the breakdown of acetylcholine, and butyrylcholine and their inhibition is regarded

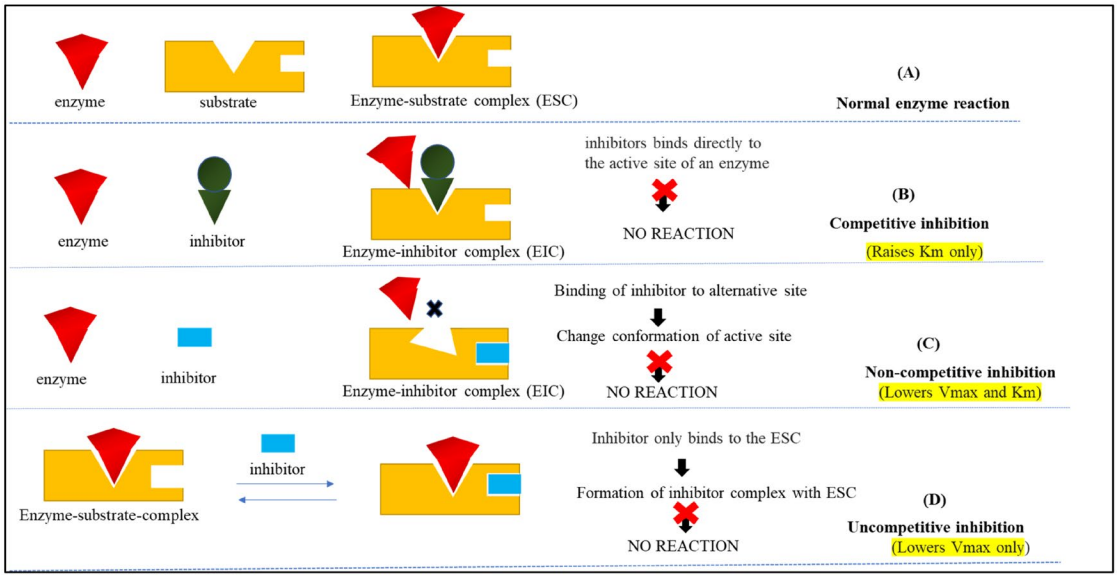

Figure 1. Schematic presentation of three reversible enzyme inhibitor reaction forms. (A) Normal enzyme reaction demonstrating lock and key model, (B) Competitive inhibition, (C) Noncompetitive inhibition, and (D) Uncompetitive inhibition. *V_{max} – maximum velocity or rate at which the enzyme-catalyzed a reaction, *K_m (Michaelis constant) is an inverse measure of affinity.

Table 1. List some important medicinal plants and their phytocompounds with key enzyme inhibition properties.

Enzymes	Phytochemicals	Plant source of these Phytochemicals	Clinical relevance	References
AChE	Quinoline alkaloids	*Skimmia laureola*, *Esenbeckia leiocarpa*, *Corydalis turtschaninovii*, *Chelidonium majus*, *Magnolia soulangiana*	Alzheimer's disease	(Rahman et al. 2006; Cardoso-Lopes et al. 2010; Hung et al. 2008; Cho, Yoo, and Kim 2006)
BChE	Sterols, terpene, glycoside	*Haloxylon recurvum*, *Pimpinella anisoides*, *Terminalia chebula*, *Micromeria cilicica*	Alzheimer's disease	(Ahmed et al. 2006; Menichini et al. 2009; Öztürk et al. 2011; Sancheti et al. 2010)
Glu/Amy	Terpenes, alkaloids, xanthones	*Fagara tessmannii*, *Cornus capitata*, *Oriciopsis glaberrima*, *Morus atropurpurea*, *Swertia mussotii*	Diabetes	(Mbaze et al. 2007; Kumar et al. 2013; Bhatia et al. 2019; Wansi et al. 2006; Tang et al. 2013; Luo et al. 2014)
Urease	Flavanones, hydroxycinnamic acids, proanthocyanidins, catechins, tannins, saponins	*Canavalia ensiformis*, *Daphne retusa*, *Pistacia atlantica*, *Scutellaria baicalensis Peumus boldus Ginkgo biloba*, *Rhus coriaria*, *Matricaria inodora*	*H. pylori*, K. pneumoniae, jack bean urease infections	(Mansoor et al. 2014; Uddin et al. 2016; Tan et al. 2013; Pastene et al. 2014; Svane et al. 2020)
XO	Quercetin derivatives, other flavonoids, flavones- chrysin, galangin, diosmetin, eupatilin, luteolin, proanthocyanidins, anthocyanidins, Jaceidin, saponins, cucurbitane triterpenoids, cajaninstilbene acid, alkaloids	Fruits/leafy vegetables, *Corylopsis coreana* Uyeki, *Nitraria retusa*, *Lagerstroemia speciosa*, *Blumea balsamifera*, *Plumula nelumbinis*, *Chrysanthemum morifolium*, *Gnaphalium affine*, *Cynara scolymus*, *Acacia confuse, Clitoria ternatea*, *Chrysanthemum sinense, Smilax riparia*, *Momordica charantia, Cajanus cajan*, *Nelumbinis folium*	Treatment of Gout	(Cao, Pauff, and Hille 2014; Zhang et al. 2018; Yoon et al. 2016; Salem et al. 2011; Unno, Sugimoto, and Kakuda 2004; Nguyen and Nguyen 2012; Ding, Ouyang, and Shen 2015; Lin, Zhang, Pan, et al. 2015; Mohos, Fliszár-Nyúl, and Poór 2020; Lin, Zhang, Pan, et al. 2015; Zhang, Zhang, et al. 2016; Qu et al. 2017; Lin et al. 2014; Sarawek et al. 2008; Tung and Chang 2010; Mehmood et al. 2019; Nguyen et al. 2006; Wu et al. 2014; Lin, Yang, and Lin 2011; Sang et al. 2017)
ACE	Indene derivatives, flavonoids	*Peperomia pellucida*	Hypertension	(Ahmad 2019; Guerrero et al. 2012)
LOX	Avenanthramides, flavonoids	Oats, *Sophora flavescens, Sideritis tragoriganum*	Asthma. atherosclerosis	(Landberg, Sunnerheim, and Dimberg 2020; Werz 2007)

Abbreviations: AChE: acetylcholinesterase; BChE: butyrylcholinesterase; GLU: glucosidase; Amy; amylase; XO: xanthine oxidase; ACE: angiotensin converting enzyme; LOX: lipoxygenase.

as one of the management strategies against several neurological problems as the cholinesterase inhibition results in an increase in the concentration of acetylcholine in the brain, which in turn causes an increase in communication between the brain nerve cells (Uysal et al. 2018). Thus, cholinesterase enzyme inhibition is one of the most effective strategies for treating Alzheimer's disease (Asghari et al. 2018). A list of secondary metabolites as enzyme inhibitors linked to neurodegenerative diseases is presented in Table 2, and their chemical structures are shown in Figure 2.

Several medicinal plants/herbs, their crude extracts/fractions, and isolated compounds have been reported for cholinesterase inhibition potential. For-example, quinoline alkaloid has major sources from *Skimmia laureola* (Rahman et al. 2006), *Esenbeckia leiocarpa* (Cardoso-Lopes et al. 2010), *Corydalis* turtschaninovii (Hung et al. 2008), *Chelidonium majus* (Cho, Yoo, and Kim 2006), *Magnolia soulangiana* (Rollinger et al. 2006), have been reported for AChE inhibition potential (Rahman et al. 2006). Likewise, for BChE inhibition, sterols from *Haloxylon recurvum* (Ahmed et al. 2006), terpenes from *Pimpinella anisoides* (Menichini et al. 2009), glycosides from *Terminalia chebula* and *Micromeria cilicica* (Öztürk et al. 2011; Sancheti et al. 2010) have been detailed for inhibition potential against this enzyme. Similarly, Ramakrishna and Roshchina (2018) have reported the isolation of α-viniferin **(1)** and kobophenol A **(2)** from *Caragana chamlague* to possess reversible noncompetitive AChE inhibition in a dose-dependent manner (IC_{50}: 2.0 and 115.8 μM, respectively) (Ramakrishna and Roshchina 2018). Boldine ((S)-2,9-dihydroxy-1,10-dimethoxyaporphine) **(3)** a natural alkaloid with reported antioxidant activity, isolated from many of the plant species from *Monimiaceae and Magnoliaceae*, have been reported for AChE and BChE inhibition activity with IC_{50} values of 372 μmol/l and BChE, 321 μmol/l, respectively (Kostelnik and Pohanka 2018). Furthermore, five compounds named artemisinin **(4)**, scopoletin **(5)**, chrysosplenetin **(6)**, eupatin **(7),** and 3-*O*-β-d-glucopyranoside of sitosterol **(8)** isolated by silica gel column chromatography from *Artemisia annua* have been studied for anti-AChE inhibition potential and

Table 2. Secondary metabolites as enzyme inhibitors linked to neurodegenerative diseases.

Test compounds	Source	AChE inhibition	BChE inhibition
α-viniferin **(1)**	*Caragana chamlague*	2.0[a]	–
kobophenol A **(2)**	*Caragana chamlague*	115.8[a]	–
Boldine **(3)**	*Monimiaceae/ Magnoliaceae species*	372[b]	321[b]
Artemisinin **(4)**	*Artemisia annua*	29.34[c]	–
Scopoletin **(5)**	*Artemisia annua*	70[c]	–
Chrysosplenetin **(6)**	*Artemisia annua*	27.14[c]	–
Eupatin **(7)**	*Artemisia annua*	67.07[c]	–
3-*O*-β-d-glucopyranoside of sitosterol **(8)**	*Artemisia annua*	37.73[c]	–
Helminthosporin **(9)**	*Rumex abyssinicus*	2.63[a]	2.99[a]
Emodin **(10)**	*Rumex abyssinicus*	15.21[a]	nd
Chrysophanol **(11)**	*Rumex abyssinicus*	33.7[a]	nd
Physcion **(12)**	*Rumex abyssinicus*	12.16[a]	nd
Arborinine **(13)**	*Ravenia spectabilis*	13.14[c]	26.34[c]
Betulinic acid **(14)**	*Chamaedorea linearis*	160[c]	108.58[c]
Ursolic acid **(15)**	*Chamaedorea linearis*	252.14[c]	309.80[c]
Cajaninstilbene acid **(16)**	*Cajanus cajan*	117.12[c]	25.82[c]
beta-sitosterol **(17)**	*Carica papaya*	208.16[c]	288.52[c]
Botulin (**18),**	*Spondias mombin*	0.88[c]	4.67[c]
Campesterol **(19)**	*Spondias mombin*	89[c]	4.08[c]
Phytol (**20)**	*Spondias mombin*	12.51[c]	23.89[c]
β-sitosterol **(17)**	*Helichrysum plicatum*		
Apigenin **(21)**	*Helichrysum plicatum*		
Nonacosanoic acid **(22)**	*Helichrysum plicatum*		
Astragalin **(23)**	*Helichrysum plicatum*		
Helichrysin A **(24)**	*Helichrysum plicatum*		
Isosalipurposide **(25)**	*Helichrysum plicatum*		
Eluptol **(26)**	*Pycnanthus angolensis*	22.26[c]	34.61[c]
Omifoate A **(27)**	*Pycnanthus angolensis*	6.51[c]	9.07[c]
Kaempferol3-*O*-(3″-*O*-E-p-coumaroyl)-(6″-*O*-E-feruloyl)-b-glucopyranoside **(28)**	*Stenochlaena palustris*	–	nd
Kaempferol 3-*O*-(3″, 6″-di-*O*-E-p-coumaroyl)-b-glucopyranoside **(29)**	*Stenochlaena palustris*	–	87.44[c]
Kaempferol 3-*O*-(6″-*O*-E-p-coumaroyl)-b-glucopyranoside **(30)**	*Stenochlaena palustris*	–	63.12[c]
Kaempferol 3-*O*-(3″-*O*-E-p-coumaroyl)-b-glucopyranoside **(31)**	*Stenochlaena palustris*	–	nd
Kaempferol 3-*O*-a-rhamnopyranoside **(32)**	*Stenochlaena palustris*	–	nd
Pyrogallol **(33)**	*Bergenia ciliata*	28[c]	70[c]
Rutin **(34)**	*Bergenia ciliata*	64[c]	116[c]
Morin **(35)**	*Bergenia ciliata*	118[c]	172[c]
Luteolin **(36)**	*Achillea monocephala*	0.014[d]	–
Naringenin **(37)**	*Achillea monocephala*	0.033[d]	–
8-hydroxysalvigenin **(38)**	*Achillea monocephala*	0.01[d]	–
Naringenin **(37)**	*Ficus thonningii/Ficus pumila*	–	–
Alpimumisoflavon **(39)**	*Ficus thonningii/Ficus pumila*	–	34.1[a]
(+)-aromadendrin **(40)**	*Ficus thonningii/Ficus pumila*	–	–
Dehydroferreirin **(41)**	*Ficus thonningii/Ficus pumila*	–	–
Bergapten **(42)**	*Ficus thonningii/Ficus pumila*	–	82.3[a]
Aviprin **(43)**	*Ficus thonningii/Ficus pumila*	–	53.5[a]
Ajaconine **(44)**	*Delphinium chitralense*	12.61[a]	10.18[a]
Delectinine **(45)**	*Delphinium chitralense*	5.04[a]	9.21[a]
Quercetin **(46)**	*Cotoneaster mongolica*	0.110[e]	–
Hyperoside **(47)**	*Cotoneaster mongolica*	0.021[e]	–
Kaempferol-5-O-β-D-glucopyranoside **(48)**	*Cotoneaster mongolica*	0.053[e]	–
Sissotrin **(49)**	*Cotoneaster mongolica*	1.530[e]	–
Ursolic acid **(15)**	*Cotoneaster mongolica*	0.306[e]	–
Euscaphic acid **(50)**	*Cotoneaster mongolica*	1.567[e]	–
Prunasin **(51)**	*Cotoneaster mongolica*	2.072[e]	–
(Z)-3-hexenyl-O-α -L-rhamnopyranosyl-(1→6)-β-D-glucopyranoside**(52)**	*Cotoneaster mongolica*	2.340[e]	–
BenzylO-α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranoside **(53)**	*Cotoneaster mongolica*	1.960[e]	-–

Abbreviations: a: μM; b: μmol/L; c: μg/mL; d: mg/mL; e: mM nd: not detected.

the compound chrysosplenetin (IC_{50}: 27.14 μg/ml) was found to be most active amongst these tested compounds (Chougouo et al. 2016). In another study, the phytochemical investigation of the ethyl acetate extract from *Rumex abyssinicus* has resulted in the isolation (by silica gel column chromatography) of four anthraquinones, namely, helminthosporin (**9**), emodin (**10**), chrysophanol (**11**), and physcion (**12**), which displayed significant inhibition of AChE with IC_{50} values of 2.63, 15.21, 33.7, and 12.16 μM, respectively. In addition, the helminthosporin was also found to inhibit BChE with an IC_{50} value of 2.99 μM. The enzyme kinetic study further conducted on helminthosporin indicated that it inhibits AChE and BChE in a noncompetitive manner with k_i values of 10.3 and 12.3 μM,

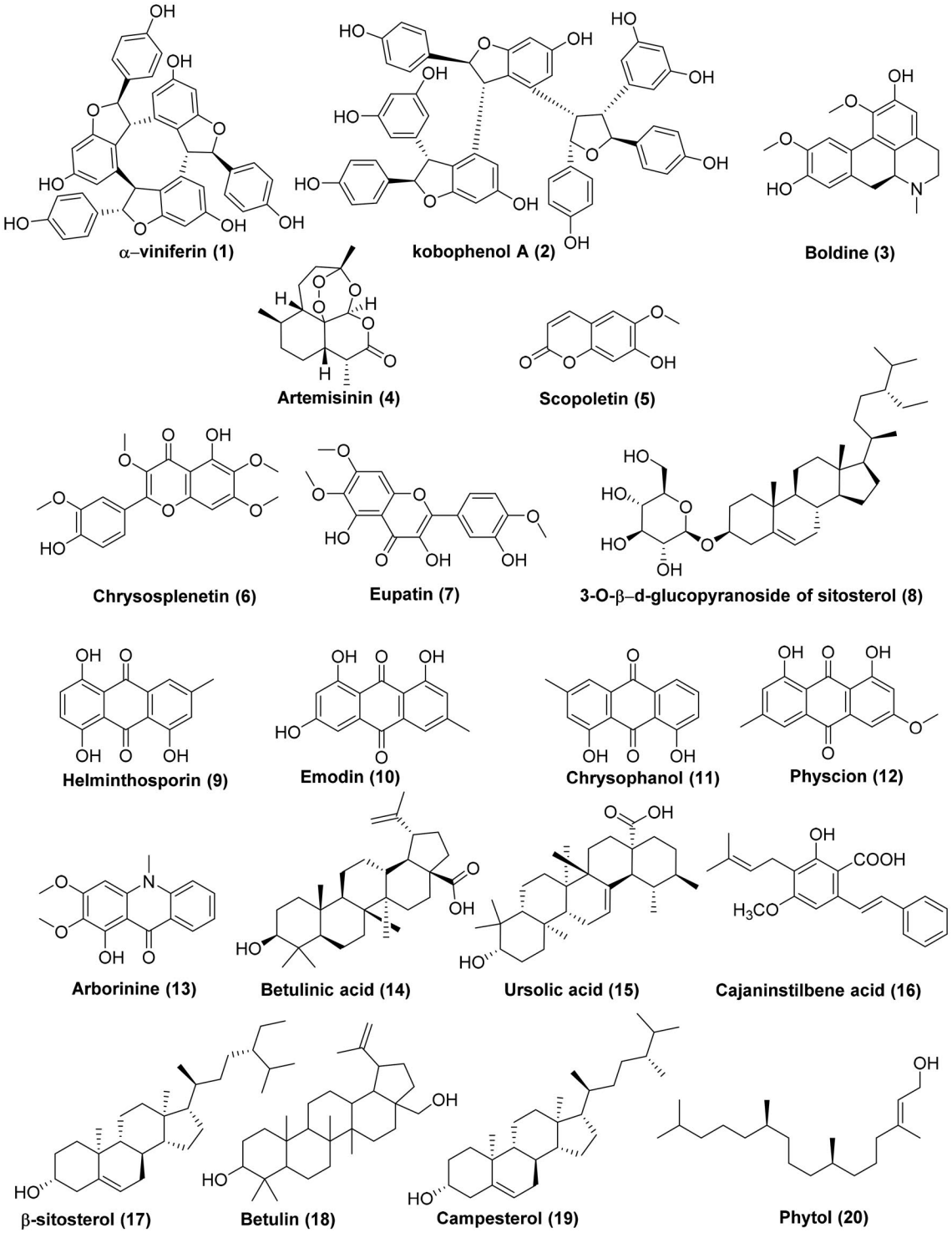

Figure 2. Chemical structures of isolated phytochemicals with cholinesterase enzyme inhibition potential.

respectively (Augustin et al. 2020). Another study evaluated the cholinesterase inhibition of arborinine **(13)** (source: *Ravenia spectabilis*), betulinic acid **(14)** (source: *Chamaedorea linearis*), ursolic acid **(15)** (source: *Chamaedorea linearis*), cajaninstilbene acid **(16)** (source: *Cajanus cajan*), beta-sitosterol **(17)** (source: *Carica papaya*). It was found that arborinine showed promising AChE inhibition (IC_{50}:13.14 μg/ml). Whereas, for BChE inhibition, arborinine and cajaninstilbene acid were the most active with IC_{50} values of 26.34 and 25.82 μg/ml, respectively (Islam et al. 2019). Elufioye et al. (2017) have presented the cholinesterase inhibitory activity of three isolated compounds (botulin (**18**), campesterol (**19**), and phytol (**20**)) from the ethyl acetate fraction of the leaves of *Spondias mombin*. The isolation procedure utilized silica gel, vacuum liquid, and preparative thin-layer chromatography techniques. The presence of cholinesterase inhibitory compounds in this plant correlates with the known memory-enhancing property of this plant and thus supports one of its uses in the ethnomedicine (Elufioye et al. 2017). Another research work

conducted on the methanol (MeOH) extract of flowers of *Helichrysum plicatum* resulted in the isolation (by silica gel column chromatography) and cholinesterase inhibition potential of eight **(17–27)** known compounds namely β-sitosterol **(17),** apigenin **(21),** nonacosanoic-acid **(22),** astragalin **(23)**, helichrysin A **(24)**, helichrysin B, and isosalipurposide **(25)**. The compounds showed IC_{50} values ranging from 1.69–2.90 and 1.09–3.89 µM against AChE and BChE, respectively (Aydin 2020). Two new bioactive compounds, named eluptol **(26)** and omifoate A **(27)**, isolated (by vacuum liquid and preparative thin layer chromatographic techniques) from the ethyl acetate fraction of leaves of *Pycnanthus angolensis* demonstrated cholinesterase inhibition potential with IC_{50} values of 22.26 µg/ml (AChE), 34.61 µg/ml (BuChE) and 6.51 µg/ml (AChE), 9.07 µg/ml (BuChE) respectively (Elufioye et al. 2016). Likewise, the MeOH extract of mature fronds from of *Stenochlaena palustris* has led to the isolation ((by vacuum liquid and preparative chromatographic techniques) of seven compounds **(28-32)**, identified as kaempferol 3-*O*-(3″-*O*-E-p-coumaroyl)-(6″-*O*-E-feruloyl)-b-glucopyranoside **(28),** kaempferol 3-*O*-(3″, 6″-di-*O*-E-p-coumaroyl)-b-glucopyranoside **(29)**, kaempferol 3-*O*-(6″-*O*-E-p-coumaroyl)-b-glucopyranoside **(30)**, kaempferol 3-*O*-(3″-*O*-E-p-coumaroyl)-b-glucopyranoside **(31),** and kaempferol 3-*O*-a-rhamnopyranoside **(32)**, which were further tested for their inhibition potential against AChE and BChE enzymes. All the tested compounds were found to be in-active against AChE while for BChE, only compounds **29**, and **30** were active with IC_{50} values of 87.44 µg/ml and 63.12 µg/ml, respectively (Chear et al. 2016). In another study, ethyl acetate fraction of *Bergenia ciliate* plant on isolation by silica gel column chromatography led to the identification of three compounds **(33-35)**, named pyrogallol **(33),** rutin **(34),** and morin **(35)** and were tested for their cholinesterase inhibition activity. The compound **33** was found to be the most active (AChE IC_{50}: 28 µg/ml BChE IC_{50}: 70 µg/ml) amongst these (Zafar et al. 2019). Another research work on the isolated compounds (luteolin **(36)**, naringenin **(37)**, and 8-hydroxysalvigenin **(38)**) from the chloroform extract (isolated by silica gel and preparative thin layer chromatographic techniques) of *Achillea monocephala* has presented the AChE inhibition activity and the compound **42** was the most active (IC_{50}: 0.01 mg/ml) (Taşkın et al. 2020). Similarly, six compounds named naringenin **(37)**, alpimumisoflavon **(39)**, (+)-aromadendrin **(40)**, dehydroferreirin **(41)**, bergapten **(42)**, aviprin **(43)** isolated (by silica gel, Sephadex LH-20, RP C18 chromatography) from methanolic extract of *Ficus thonningii* and *Ficus pumila* were tested for AChE and BChE inhibition potential. All of these tested compounds were found inactive against AChE, while for BChE, compounds **38**, **42**, and **43** were found to be active with IC_{50} values of 34.1, 82.3, and 53.5 µM, respectively (Fys, et al. 2017). The cholinesterase inhibition potential of two alkaloids, one atisine type C-20 diterpenoid alkaloid ajaconine **(44)** and the other lycoctonine type C-19 diterpenoid alkaloid delectinine **(45)** isolated (by silica gel and flash silica gel chromatography) from *Delphinium chitralense*, were found to have inhibition capacity against AChE with IC_{50} value of 12.61 µM (compound **44**) and 5.04 µM (compound **45**). In contrast, for BChE, the IC_{50} values were 10.18 µM (compound **44**) and 9.21 µM (compound **45**) (Ahmad et al. 2016). From the *n*-butanol fraction of leaves of *Cotoneaster mongolica* the following compounds (**46-53**), namely quercetin **(46),** hyperoside **(47),** kaempferol-5-*O*-β-D-glucopyranoside **(48),** sissotrin **(49),** ursolic acid **(15),** euscaphic acid **(50),** prunasin **(51),** (Z)-3-hexenyl-*O*-α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranoside **(52)**, and benzyl *O*-α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranoside **(53)** were isolated by silica gel and Sephadex LH-20 chromatography, and tested for anti-AChE inhibition and the compound **47** was found to be most active with IC_{50} value of 0.021 mM (Gendaram 2019). Nevertheless, it is notable that most of the cholinesterase inhibition testing reported above are *in vitro* activities, and similar results do not guarantee *in vivo* evaluations. The cholinesterase inhibition potential of the isolated compounds and *in-vivo* testing may contribute toward more credible results which should be planned in future studies.

α-Glucosidase and α-amylase inhibitors: diabetes

Diabetes is a multifactorial metabolic disorder characterized by aberrant carbohydrate metabolism and high glucose levels. Alarmingly, the WHO has predicted diabetes to be the 7th leading cause of death by 2030, with the expected rise in the diabetic population to 418 million in 2025 and 552 million by 2030 (Federation 2019). Diabetes mellitus is an important metabolic problem characterized by insulin deficiency or no response to insulin in cells (Kumaresan, Jeyanthi, and Kalaivani 2014). Diabetes mellitus is categorized as a complex metabolic disease associated with irregular insulin production, developing insulin resistance, and β-cell malfunction. The intestinal absorption and breakdown of carbohydrates are majorly regulated by the enzymes α-amylase and α-glucosidase. A major intention is to discover natural α-amylase and α-glucosidase enzyme inhibitors (Asghari et al. 2018). Inhibitors of α-amylase and α-glucosidase are becoming the target enzymes for possible drug development. These enzymes play a key role in hydrolyzing long-chain carbohydrates and disaccharides into monosaccharides, respectively (Jhong et al. 2015). The literature has a number of documentation that identify plant extracts as a viable source to relieve diabetes and through inhibitory actions against amylase and glucosidase. Despite these findings, there is still an ongoing need to study novel plant sources as antidiabetic medications. A mechanistic representation of the mechanism of action involved in amylase and glucosidase associated with diabetes control is shown in Figure 3.

Previously, terpenes (Mbaze et al. 2007; Kumar et al. 2013; Bhatia et al. 2019) from *Fagara tessmannii* (Mbaze et al. 2007; Kumar et al. 2013) and *Cornus capitata* (Bhatia et al. 2019), alkaloids (Wansi et al. 2006; Tang et al. 2013) from *Oriciopsis glaberrima* (Wansi et al. 2006), *Morus atropurpurea* (Tang et al. 2013) and xanthones (Luo et al. 2014)

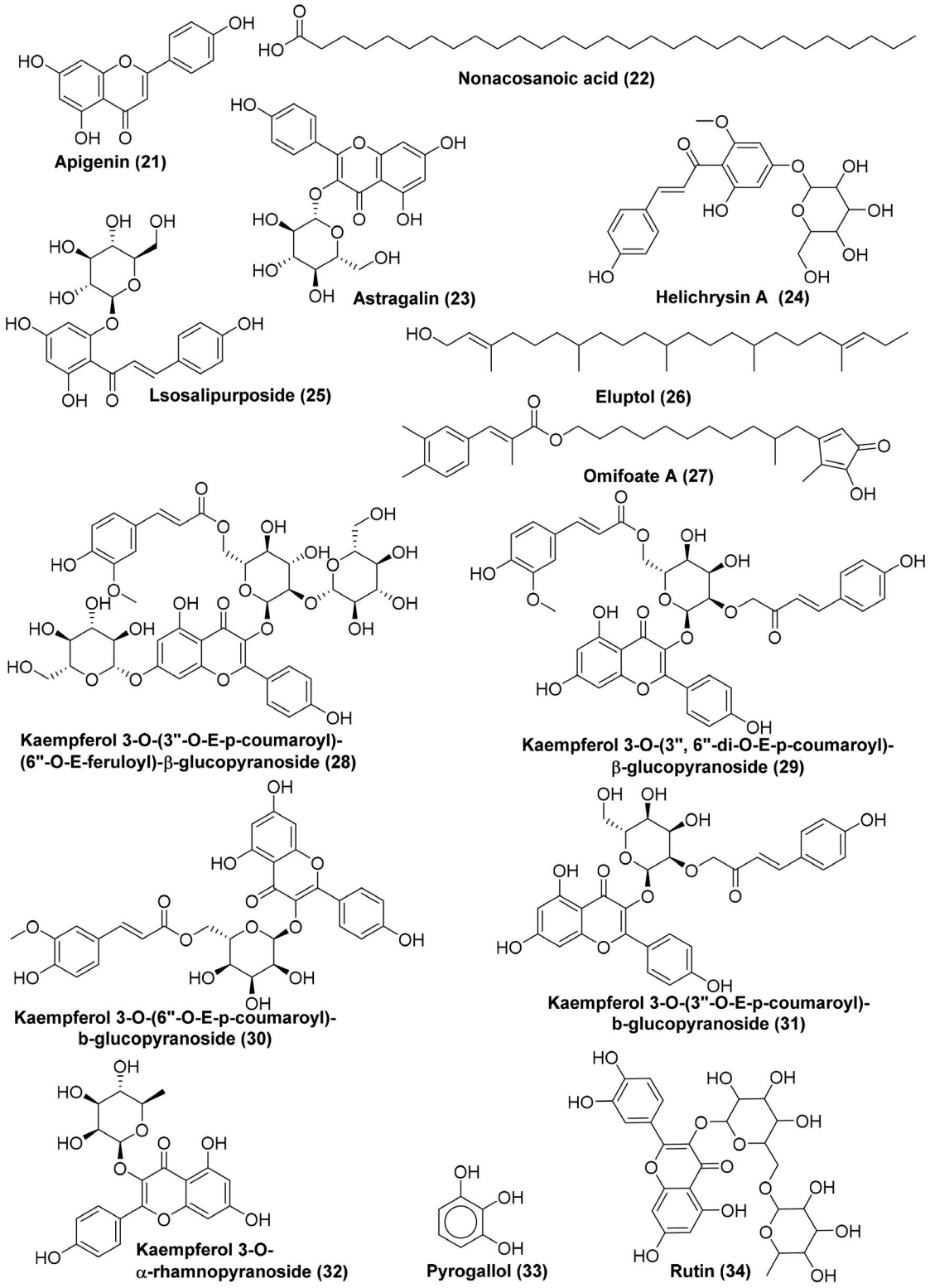

Figure 3. Mechanistic representation of the amylase, glucosidase, and HMG-CoA reductase enzyme to control diabetes and cardiovascular disorders, respectively.

from *Swertia mussotii* (Luo et al. 2014) plant species have been studied for glucosidase inhibition potential. Likewise, Meng et al. (2009) reported the *in vivo* activity of *Caragana intermedia* to control blood glucose levels (Meng et al. 2009) and similarly, *Caragana arborescens* has been reported to contain flavonoids having hypoglycemic properties (Mandal et al. 2015). Traditional medicinal plants have been efficiently utilized as antidiabetic agents for ages owing to their wide range of phytochemicals. Particularly, plant-derived chemical groups i.e., alkaloids, sesquiterpene and saponins, flavonoids, dietary fibers, ferulic acid, tannins, limonene, and oleuropeoside have shown promising antidiabetic effects

Table 3. Natural products having α-amylase/α-glucosidase inhibitory activities.

Test compounds	Source	Amylase	Glucosidase
Oleanolic acid **(54)**	*Syzygium aromaticum*	3.60[a]	12.40[a]
Acetogenin	*Annona muricata*	27.86[b]	27.86[b]
Epigallocatechin-3-*O*-gallate **(55)**	*Camellia sinensis*	–	19.5[c]
Mangiferin **(56)**	*Moringa indica*	–	36.84[d]
Luteolin 7-*O*-glucoside **(57)**	*Capcicum annuum*	20[d]	30[d]
bicyclo[2.2.0]hexane-2,3,5-triol **(58)**	*Khaya senegalensis*	63.3[d]	45.9[d]
3β-O-acetyl betulinic acid **(59)**	*Cassia singueana*	98.5[d]	45.1[d]
2,7-dihydroxy-4H-1-benzopyran-4-one **(60)**	*Ziziphus mucronata*	93.7[d]	39.0[d]
Wednenic **(61)**	*Wedelia chinensis*	436.8[d]	915.6[d]
Jaceosidin **(62)**	*Wedelia chinensis*	112.8[d]	785.9[d]
Pomonic acid **(63)**	*Wedelia chinensis*	420.7[d]	na
Pomolic acid **(64)**	*Wedelia chinensis*	395.6[d]	821.4[d]
Gymnemic Acid IV **(66)**	*Gymnema sylvestre*	–	68.70[d]
Myricetin **(65)**	*Hovenia dulcis*	662[d]	3[d]
Quercetin	*Hovenia dulcis*	770[d]	32[d]
Osthole **(67)**	*Ferulago bracteate*	–	0.95[e]
Imperatorin **(68)**	*Ferulago bracteate*	–	1.23[e]
Prantschimgin **(69)**	*Ferulago bracteate*	–	1.86[e]
Suberosin **(70)**	*Ferulago bracteate*	–	0.89[e]
Xanthotoxin **(71)**	*Ferulago bracteate*	–	5.38[e]
Felamidin **(72)**	*Ferulago bracteate*	–	0.42[e]
Umbelliferone **(73)**	*Ferulago bracteate*	–	9.32[e]
Carnosol **(74)**	*Salvia aurita*	19.8[d]	51.8[d]
Rosmanol **(75)**	*Salvia aurita*	40.9[d]	16.4[d]
7-methoxyrosmanol **(76)**	*Salvia aurita*	na	4.2[d]
12-methoxycarnosic acid **(77)**	*Salvia aurita*	16.2[d]	36.9[d]
4,7- dimethylapigenin **(78)**	*Salvia aurita*	na	28.7[d]
19-acetoxy-12- methoxycarnosic acid **(79)**	*Salvia africana-lutea*	na	na
3β-acetoxy-7α-methoxyrosmanol **(80)**	*Salvia africana-lutea*	na	na
Oleanolic acid	*Salvia africana-lutea*	12.5[d]	22.9[d]
Ursolic acid	*Salvia africana-lutea*	66.1[d]	11.3[d]
11,12-dehydroursolic acid lactone **(81)**	*Salvia africana-lutea*	na	85.8[d]
β-amyrin **(82)**	*Salvia africana-lutea*	76.6[d]	17.1[d]
Katononic acid **(83)**	*Nuxia oppositifolia*	52.4[d]	88.6[d]
3-oxolupenal **(84)**	*Nuxia oppositifolia*	46.2[d]	62.3[d]
β-sitosterol	*Helichrysum plicatum*		
Apigenin	*Helichrysum plicatum*		
Nonacosanoic acid	*Helichrysum plicatum*		
astragalin	*Helichrysum plicatum*		
β-sitosterol-3-*O*-β-D-glucopyranoside	*Helichrysum plicatum*		
Helichrysin A	*Helichrysum plicatum*		
Helichrysin B	*Helichrysum plicatum*		
Isosalipurposide	*Helichrysum plicatum*		
1-methylene-7-(prop-1-en-2-yl)-octahydronapthalen2 (1H)-one **(85)**	Miscellaneous phytocompounds		
3,8-dimethyl-1-oxo-1,3q,4,5,6,7-hexahydroazulen-5-yl)acrylate **(86)**	Miscellaneous phytocompounds		

Abbreviations: a: mmol/L; b: mg/dL; c: μM; d: μg/mL; e: mg/mL.

(Alam et al. 2019). Ample evidence exists on the potential of crude extracts of *Syzygium aromaticum* (clove) to inhibit blood glucose levels by down-regulating α-glucosidase and α-amylase in rats (Zulcafli et al. 2020) and in healthy/pre-diabetic human volunteers (Randomised Clinical Trial) (Mohan et al. 2019). A list of secondary metabolites as enzyme inhibitors linked to diabetes is presented in Table 3 and their chemical structures are shown in Figure 4.

A triterpene, oleanolic acid **(54)** from clove (*Syzygium aromaticum*) demonstrated promising activity against α-amylase (IC_{50}: 3.60 mmol/L) and α-glucosidase (IC_{50}: 12.40 mmol/L) in the small intestine of STZ-induced diabetic rats (Khathi et al. 2013). Another latest study on rats has shown powerful antidiabetic effects of the fruit pulp and leaf of *Annona muricata* (Soursop) by inhibiting α-amylase and α-glucosidase activity. Among the active ingredients, isolated compound acetogenin (15-acetyl guanacone) isolated from the fruit pulp exhibited superior antidiabetic effects owing to their target enzyme specificity and higher IC_{50} (27.86 mg/dL), *Bmax* and *Vmax* and lower *Kd* values. Notably, the binding of acetogenin to the active site of α-amylase and α-glucosidase gave better binding energies than metformin. This demonstrates the discovery of safer antidiabetic drugs from plant sources can improve the management of diabetes (Agu et al. 2019).

Promisingly, epigallocatechin-3-*O*-gallate **(55)** extracted from the tea plant (*Camellia sinensis*) showed higher inhibitory activity against α-glucosidase (IC_{50}:19.5 μM) compared to acarbose (IC_{50}: 278.7 μM) (Xu et al. 2019). Furthermore, mangiferin **(56)** extracted from mango pulp (*Moringa indica*) slowed glucose metabolism by inhibiting α-glucosidase and α-amylase enzymes. The IC50 of mangiferin was 36.84 μg/ml compared to the standard acarbose, 21.33 μg/ml (Sekar et al. 2019). Another research work highlighted the amylase (IC_{50}: 20 μg/ml) and glucosidase (IC_{50}: 30 μg/ml) inhibition potential of luteolin 7-*O*-glucoside **(57)** isolated from water extract of pepper (*Capsicum annum*) (Park et al. 2016). Three African medicinal plants om isolation resulted in the identification of bicyclo hexane-2,3,5-triol **(58)** (isolated from the butanol fraction

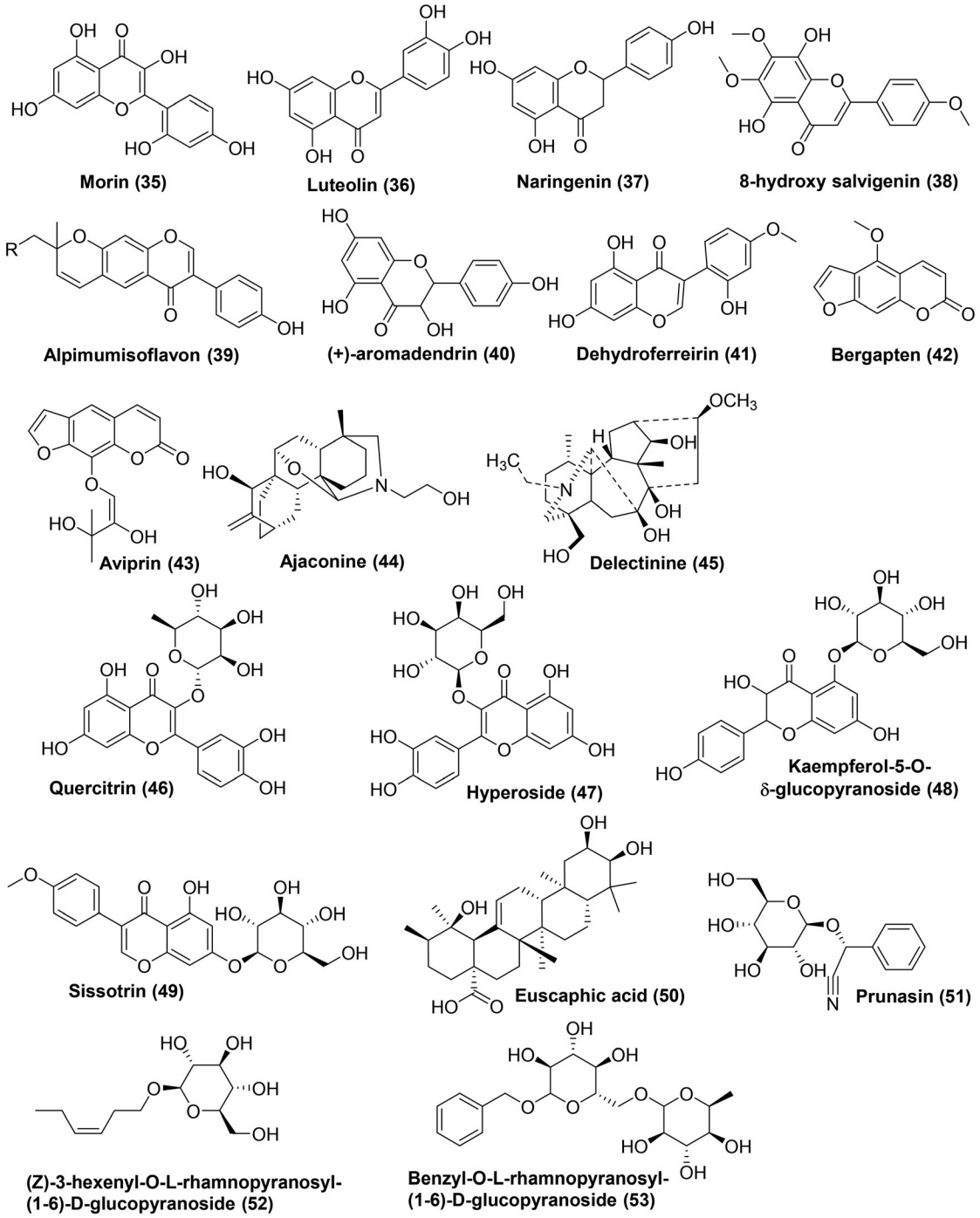

Figure 4. Natural products with α-amylase and α-glucosidase inhibitory activities. (a) Chemical structures of isolated phytochemicals with anti-diabetic enzyme inhibition potential.

of *Khaya senegalensis root)*, 3β-*O*-acetyl betulinic acid **(59)** (isolated from the acetone fraction of the stem bark of *Cassia singueana),* and 2,7dihydroxy-4H-1-benzopyran-4 -one **(66)** (isolated from the acetone fraction *Ziziphus mucronate root)*, as the bioactive compounds. The isolation was done using silica gel column chromatography. These compounds demonstrated a significant ($p < 0.05$) inhibitory effect on α-glucosidase and α-amylase activities than acarbose (Ibrahim et al. 2017). The ethyl acetate fraction from the leaves of *Wedelia chinensis* has led to the isolation (by silica gel and Sephadex LH-20 column chromatography) of few compounds, named wednenic **(61),** jaceosidin **(62),** pomonic acid **(63),** and pomolic acid **(64)** which were tested for their α-amylase and α-glucosidase inhibition potential. The compound **62** showed the strongest effect with IC_{50} values of 112.8 µg/ml (against α-amylase) and 785.9 µg/ml (against α-glucosidase) (Thao et al. 2018). Gymnemic Acid IV **(66)** from *Gymnema sylvestre* is responsible for inhibitory activity against yeast alpha-glucosidase with an IC_{50} of 68.70 µg/ml (Alam et al. 2019). Myricetin showed an IC_{50} of 662 µg/ml against alpha- amylase and 3 µg/ml against alpha-glucosidase. Quercetin showed an IC_{50}

of 770 µg/ml against alpha-amylase and 32 µg/ml against alpha- glucosidase (Meng et al. 2016). A number of compounds, osthole **(67),** imperatorin **(68),** prantschimgin **(69),** suberosin **(70),** xanthotoxin **(71)**, felamidin **(72),** umbelliferone **(73),** isolated (by silica gel column chromatography) from the roots of *Ferulago bracteate* were tested for the amylase and glucosidase inhibition potential. Amongst these tested compounds showed the inhibition potential in increasing order with IC_{50} values of 0.89, 0.95, 1.23, 1.86, and 3.24 mg/mL (Karakaya et al. 2018). The phytochemical investigation of crude MeOH extract of *Salvia aurita* yielded four known abietane diterpenes, namely carnosol **(74)**, rosmanol **(75),** 7-methoxyrosmanol **(76),** and 12-methoxycarnosic acid **(77)** and one flavonoid named 4,7- dimethylapigenin **(78)**. The isolation was achieved *via* silica gel, preparative HPLC and HPLC techniques. The biological evaluation of the isolated compound against alpha-glucosidase exhibited strong inhibitory activities for **76** and **75** with IC_{50} values of 4.2 and 16.4 µg/mL, respectively. At the same time, **77** and **74** demonstrated strong alpha-amylase inhibitory activity amongst the isolated compounds with IC_{50} of 16.2 ± 0.3 and 19.8 ± 1.4 µg/mL, respectively (Etsassala, et al. 2020). The methanolic extract of *Salvia africana-lutea* on isolation (by using silica gel column chromatography and HPLC), afforded new abietane diterpenes, namely 19-acetoxy-12- methoxycarnosic acid **(79)**, 3β-acetoxy-7α-methoxyrosmanol **(80),** in addition to known triterpenes, oleanolic, and ursolic acids, 11,12-dehydroursolic acid lactone **(81)** and β-amyrin **(82)**. The *in vitro* bio-evaluation against alpha-glucosidase showed strong inhibitory activities, while oleanolic acid demonstrated the strongest *in vitro* alpha- amylase inhibitory activity among the tested compounds with IC_{50} of 12.5 µg/mL (Etsassala et al., 2019). The *n*-hexane fraction *Nuxia oppositifolia* led to the isolation (by using silica gel column chromatography) of katononic acid **(83)** and 3-oxolupenal **(84)**, and their antidiabetic activities were assessed by α-amylase and α-glucosidase enzyme inhibition. 3-oxolupenal and katononic acid showed IC_{50} values of 46.2 µg/mL (101.6 µM) and 52.4 µg/mL (119.3 µM), respectively against the amylase inhibition. 3-oxolupenal (62.3 µg/mL or 141.9 µM) exhibited more potent inhibition against α-glucosidases compared to katononic acid (88.6 µg/mL or 194.8 µM) (Alqahtani et al. 2019). Another research work conducted on the methanol (MeOH) extract of flowers of *Helichrysum plicatum* resulted in the isolation (by silica gel column chromatography) and cholinesterase inhibition potential of eight known compounds namely *β*-sitosterol, apigenin, nonacosanoic acid, astragalin, *β*-sitosterol-3-*O*-*β*-D-glucopyranoside, helichrysin A, helichrysin B, and isosalipurposide. The IC_{50} values of *H. plicatum* DC. subsp. MeOH extract for hCAI, hCAII, AChE, BChE, and α-glycosidase were found to be 77.87, 52.90, 115.50, 117.46, and 81.53 mg/mL, respectively. The compounds showed IC_{50} values of 1.43–4.47, 1.40–4.32, 1.69–2.90, 1.09–3.89, and 1.61–3.80 µM against hCAI, hCAII, AChE, BChE, and α-glycosidase, respectively. In summary, *H. plicatum* secondary metabolites demonstrated strong inhibitory effects especially against hCAI and hCAII, whereas the MeOH extract showed a weak inhibitory effect on all enzymes (Aydin 2020). Similarly, some of the other plant phytochemicals inclusing 1-methylene-7-(prop-1-en-2-yl)-octahydronapthalen2 (1H)-one **(85)**, and 3,8-dimethyl-1-oxo-1,3q,4,5,6,7-hexahydroazulen-5-yl)acrylate **(86)** are also reported for the anti-diabetic activities. However, in most of the studies, only one dose of extract/isolated compound was administered; therefore, a dose-dependent effect was not observed in the results. It should also be considered that the pharmacological relevance of the *in vitro* assays has not been proven; therefore, both *in vitro* and *in vivo* animal models must be employed to demonstrate the anti-diabetic activity of these extracts and isolated phytochemicals.

Urease inhibitors

Urease is one of the major enzymes responsible for killing *H. pylori* in the stomach. It is the leading cause of many gastrointestinal diseases, for example, gastric cancer, peptic, duodenal, and gastritis ulcer (Mahernia et al. 2015). Flavones, flavanones, and hydroxycinnamic acids (Mansoor et al. 2014; Uddin et al. 2016; Tan et al. 2013) obtained from different plant sources, namely Canavalia ensiformis (Sehgal and Naylor 1966), *Daphne retusa* (Mansoor et al. 2014), Pistacia atlantica (Uddin et al. 2016) and Scutellaria baicalensis (Tan et al. 2013) have been reported to possess urease inhibition potential. A list of secondary metabolites as urease enzyme inhibitors is presented in Table 4, and their chemical structures are shown in Figure 5.

Inhibition potential of confertin (**87**), and scopoletin (**88**) isolated ethyl acetate fraction (by silica gel column chromatography) of *Hypochaeris radicata* was carried out against urease enzyme. The compounds (**87–88**) exhibited selective activity against urease enzyme with an IC_{50} value of 24.12, and 30.12 µM, respectively (Abu-Izneid et al. 2020). Three flavanonol namely quercetin, dihydroquercetin **(89),** and dihydromyricetin **(90)** were isolated by column chromatography from ethyl acetate fraction of *Picea smithiana* were evaluated for their enzyme inhibition potential against urease. Compound **90** showed significant activity against urease with an IC_{50} value of 29.73 µM, While quercetin and **89** were found to be weak inhibitors of urease with IC_{50} values of 208.87 and 202.87 µM, respectively (Kashif Bashir et al. 2017). Phytochemical studies by using silica gel column chromatography on *Dactyladenia floribunda* Welw furnished twelve known compounds including *β*-sitosterol, lupeol **(91),** betulinol **(92),** betulinic acid, hennadiol **(93),** ursolic acid, and hexane-1,2,3,4,5,6-hexol **(94),** and also reported their ani-urease activity. Out of these tested compounds, only compounds *β*-sitosterol **17** (IC_{50}: 20.04 µM), ursolic acid (IC_{50}: 78.9 µM), and **94** (IC_{50}: 43.6 µM) were found to be active, while the rest of the compounds were found to be inactive (Adjapmoh Essombo et al. 2017). The chloroform extract of *Achillea monocephala* on bio-activity-guided isolation by silica gel column chromatography led to the identification of compounds luteolin **(40),** naringenin (**41),** and 8-hydroxysalvigenin **(42)**, which were furthest tested for their urease enzyme inhibition potential. It possessed anti-urease potential with IC_{50} values of 1.20, 0.083, and

Table 4. Secondary metabolites having anti-urease activity.

Test compounds	Source	Urease inhibition
Confertin **(87)**	*Ferulago bracteate*	24.12 [a]
Scopoletin **(88)**	*Ferulago bracteate*	30.12 [a]
Quercetin	*Picea smithiana*	208.87 [a]
Dihydroquercetin **(89)**	*Picea smithiana*	202.87 [a]
Dihydromyricetin **(90)**	*Picea smithiana*	29.73 [a]
β-sitosterol	*Dactyladenia floribunda*	20.4 [a]
Lupeol **(91)**	*Dactyladenia floribunda*	Na
Betulinol **(92)**	*Dactyladenia floribunda*	Na
Betulinic acid	*Dactyladenia floribunda*	Na
Hennadiol **(93)**	*Dactyladenia floribunda*	Na
Ursolic acid	*Dactyladenia floribunda*	78.9 [a]
Hexane-1,2,3,4,5,6-hexol **(94)**	*Dactyladenia floribunda*	43.6 [a]
Luteolin **(40)**	*Achillea monocephala*	1.20 [b]
Naringenin **(41)**	*Achillea monocephala*	0.083 [b]
8-hydroxysalvigenin **(42)**	*Achillea monocephala*	0.043 [b]
Izalpinin **(95)**	*Iris loczyi*	358.23 [a]
Irilin D **(96)**	*Iris loczyi*	69.43 [a]
5,7-Dihydroxy-2′,6-dimethoxyisoflavone **(97)**	*Iris loczyi*	95.53 [a]
Irilin B **(98)**	*Iris loczyi*	138.70 [a]
Irisoid A **(99)**	*Iris loczyi*	17.60 [a]
4′,5,7-Trihydroxy-6-methoxyflavanone **(100)**	*Iris unguicularis*	367.86 [a]
Tectorigenin **(101)**	*Iris unguicularis*	170.60 [a]
4′,5,7-Trihydroxy-3′,8-dimethoxyflavanone **(102)**	*Iris unguicularis*	58.46 [a]
8-Methoxyeriodictyol **(103)**	*Iris unguicularis*	70.96 [a]
Hispidulin **(104)**	*Iris unguicularis*	76.20 [a]
Eupafolin **(105)**	*Iris unguicularis*	40.83 [a]
Tectorigenin-4′-glucoside **(106)**	*Iris unguicularis*	189.16 [a]
Mangiferin **(107)**	*Iris unguicularis*	152.20 [a]
1,3-*O*-Diferuloylsucrose **(108)**	*Iris unguicularis*	322.76 [a]

Abbreviations: a: μM; b: mg/mL.

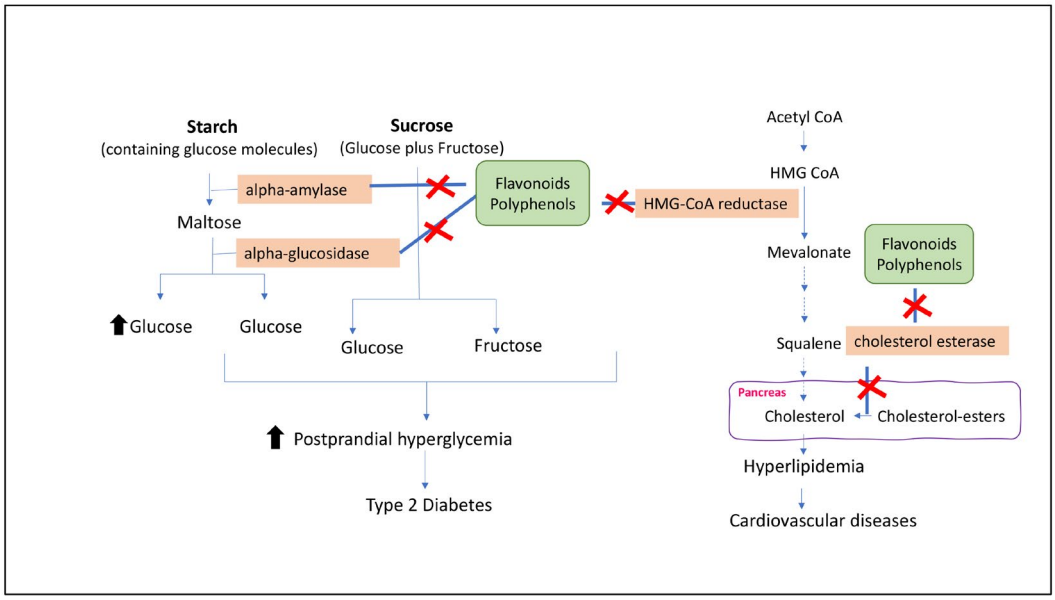

Figure 5. Chemical structures of isolated phytochemicals with anti-lipase inhibition potential.

0.043 mg/ml, respectively (Taşkın et al. 2020). Saleem, Zengin, et al. (2019) reported the anti-urease activity of the isolated phytochemicals (**95–108**) from the aqueous ethanolic extract of two species of *Iris, that is, Iris loczyi* and *Iris unguicularis*. The isolation was done using vacuum liquid chromatography (VLC) on silica gel. The isolated compounds form *Iris loczyi* plant which showed urease inhibition potential were izalpinin (**95**), irilin D (**96**), 5,7-dihydroxy-2′,6-dimethoxyisoflavone (**97**), irilin B (**98**), irisoid A (**99**), whereas the compounds 4′,5,7-trihydroxy-6-methoxyflavanone (**100**), tectorigenin (**101**), 4′,5,7-trihydroxy-3′,8-dimethoxyflavanone (**102**), 8-methoxyeriodictyol (**103**), hispidulin (**104**), eupafolin (**105**), tectorigenin-4′-glucoside (**106**), mangiferin (**107**), and 1,3-*O*-diferuloylsucrose (**108**) were isolated from *Iris unguicularis*. Amongst these isolated compounds, compound **102** was found to be most active (IC_{50}: 58.46 μM) (Saleem, Zengin, et al. 2019). Overall, it was noted that urease is responsible for causing several gastrointestinal diseases, including gastric cancer, gastritis ulcer, and peptic ulcer. The phytocompounds such as flavones,

flavanones, and hydroxycinnamic acids obtained from various plants, including *Canavalia ensiformis*, *Daphne retusa*, *Pistacia atlantica*, and *Scutellaria baicalensis*, have been reported to possess urease inhibition potential.

Lipase inhibitors: obesity

Being overweight and obesity are primarily linked with the increased incidence of chronic diseases, including diabetes, cardiovascular diseases and cancer. Out of several therapeutic options, one is the inhibition of gastrointestinal lipase. Orlistat is a clinically available drug that exhibits anti-obesity effects by inhibiting gastric and pancreatic lipase, but its use has decreased due to the side impacts. Pancreatic lipase is the key lipid absorption enzyme and the most attractive therapeutic target against obesity (Endalifer and Diress 2020). A list of secondary metabolites as enzyme inhibitors linked to lipase is presented in Table 5, and their chemical structures are shown in Figure 6.

Gallic acid **(109)** and 4-hydroxy benzoic acid **(110),** as identified from *Mangifera indica,* showed anti-lipase activity with IC_{50} values of 0.47 and 1.1.5 nM (De Pradhan et al. 2017). Plumbagin (**111**) is a naphthoquinone found in the roots of *Plumbago zeylanica,* was evaluated for its anti-obesity activity and presented the IC_{50} value of 82.08 µM against pancreatic lipase enzyme (Pai et al. 2018). Three polyphenolic compounds (quercetin, *p*-coumaric acid **(112)**, and caffeic acid **(112)**) identified from hot pepper (Piper nigrum) were found to have lipase inhibition potential with IC_{50} values of 6.1, 170.2, and 401.5 µM, respectively (Martinez-Gonzalez et al. 2017). Bioactivity-guided isolation of natural compounds (by using silica gel column chromatography and RP-HPLC techniques) from the pericarps of *Garcinia mangostana*, using a pancreatic lipase assay, led to the identification of xanthones including α-mangostin (**114**), β-mangostin **(115)**, γ-mangostin (**116**), 1-isomangostin (**117**), gartanin (**118**), garcinone D (**119**), 9-hydroxycalabaxanthone (**120**), smeathxanthone A (**121**), tovophyllin A (**122**), 8- deoxygartanin (**123**), mangostanin (**124**), calocalabaxanthone (**125**), and 1,7-dihydroxy-3-methoxy-2-(3-methylbut-2-enyl) xanthen-9-one (**126**). The inhibitory activities of the isolated xanthones against pancreatic lipase were evaluated and α-mangostin was found to possess the most potent inhibitory activity (IC_{50}: 5.0 µM) in a non-competitive manner, compared with the positive control, orlistat (IC_{50}: 3.9 µM) (Chae et al. 2016). The ethanolic extract (EtOH) of the peels of *Annona crassiflora* fruits was subjected to isolation by using silica gel column chromatography and semi-preparative HPLC techniques, which yielded stephalagine (1,2-methylenedioxy-3-methoxyaporphine) **(127),** an aporphine alkaloid, was identified. The compound **127** was further evaluated as a pancreatic lipase inhibitor (IC_{50}: 8.35 µg/mL) (Pereira et al. 2017). These studies demonstrate the potential of natural compounds to inhibit pancreatic lipase. Gallic acid, 4-hydroxy benzoic acid, plumbagin, quercetin, p-coumaric acid, caffeic acid, α-mangostin, gartanin, garcinone D, 9-hydroxycalabaxanthone, smeathxanthone A, tovophyllin A, 8-deoxygartanin, mangostanin, calocalabaxanthone, and stephalagine have all demonstrated inhibitory activity against pancreatic lipase in various studies. Mangostin and gallic acid exhibited the most potent inhibitory activity among these compounds. These findings suggest that natural compounds that inhibit pancreatic lipase could be developed into effective anti-obesity agents. To evaluate the safety and efficacy of these compounds for human use, additional research is required

Inflammation

Lipoxygenase is an enzyme that can generate lipid mediators including leukotrienes and prostaglandins, ultimately provoking many inflammatory disorders (Perera et al. 2018; Schneider and Bucar 2005). Lipoxygenase enzyme is involved in inflammation, particularly in the biochemical processes of leukotrienes which are the primary triggers for allergic reactions and inflammation (Ahmed et al. 2006).

Table 5. Secondary metabolites as enzyme inhibitors linked to lipase.

Test compounds	Source	Pancreatic lipase
Gallic acid **(109)**	*Mangifera indica*	0.47 [a]
4-hydroxy benzoic acid **(110)**	*Mangifera indica*	1.15 [a]
Plumbagin **(111)**	*Plumbago zeylanica*	14.51 [b]
Quercetin	*Piper nigrum*	6.1 [c]
p-coumaric acid **(112)**	*Piper nigrum*	170.2 [c]
Caffeic acid **(113)**	*Piper nigrum*	401.5 [c]
α-mangostin (**114**)	*Garcinia mangostana*	5 [c]
β-mangostin **(115)**	*Garcinia mangostana*	27.5 [c]
γ-mangostin (**116**)	*Garcinia mangostana*	10 [c]
1-isomangostin (**117**)	*Garcinia mangostana*	34.5 [c]
Gartanin (**118**)	*Garcinia mangostana*	12 [c]
Garcinone D (**119**)	*Garcinia mangostana*	22.5 [c]
9-hydroxycalabaxanthone (**120**)	*Garcinia mangostana*	12 [c]
Smeathxanthone A (**121**)	*Garcinia mangostana*	19.5 [c]
Tovophyllin A (**122**)	*Garcinia mangostana*	12.5 [c]
8- deoxygartanin (**123**)	*Garcinia mangostana*	>50 [c]
Mangostanin (**124**)	*Garcinia mangostana*	21 [c]
Calocalabaxanthone (**125**)	*Garcinia mangostana*	>50 [c]
1,7-dihydroxy-3-methoxy-2-(3-methylbut-2-enyl) xanthen-9-one (**126**)	*Garcinia mangostana*	5.5 [c]
Stephalagine **(127)**	*Annona crassiflora*	8.35[d]

Abbreviations: a: nM, b: µg, c: µM; d: g/mL.

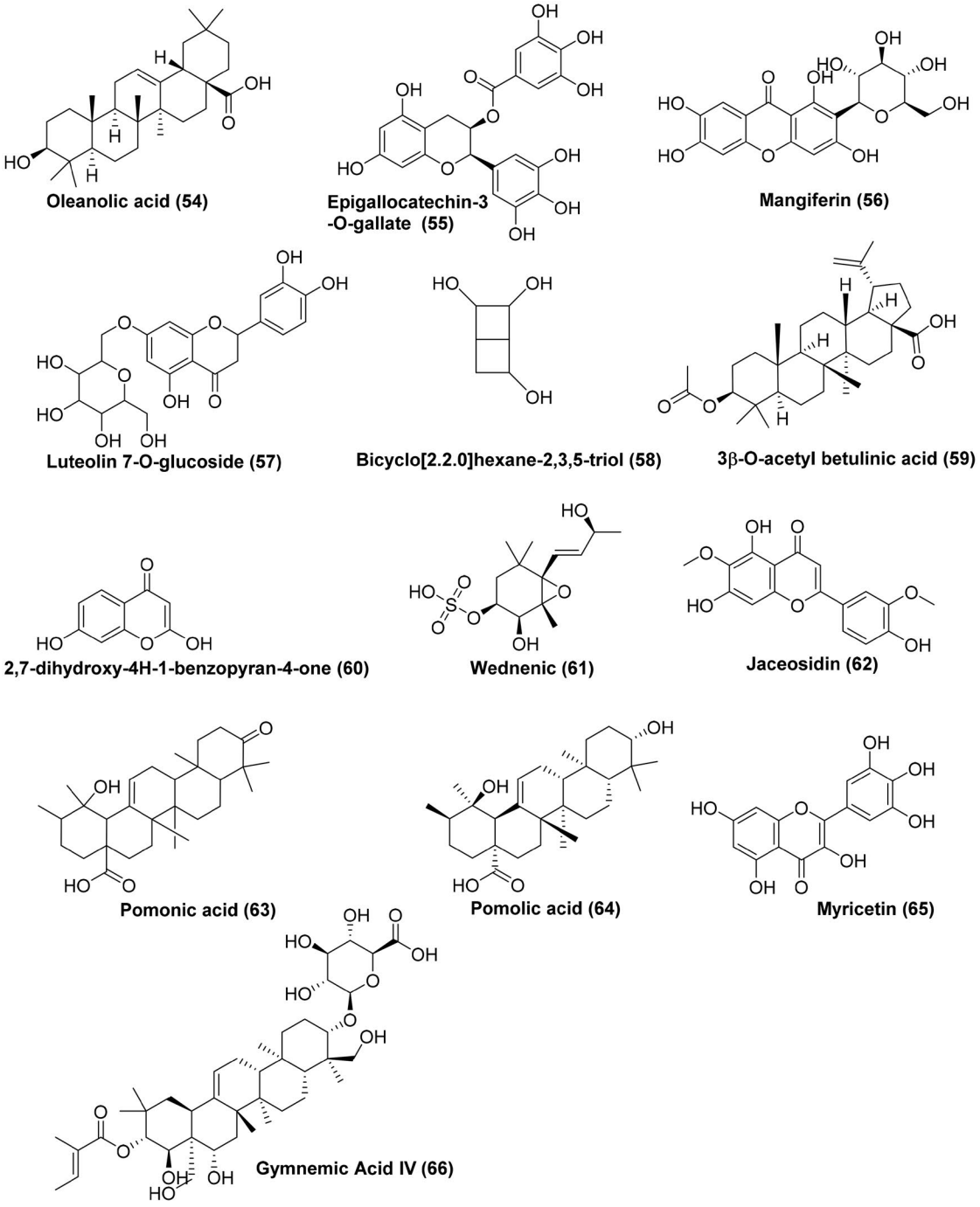

Figure 6. Chemical structures of Secondary metabolites as enzyme inhibitors linked to lipase.

Lipoxygenases (LOXs) are potential treatment targets in various inflammatory conditions. It is assumed that blocking the arachidonic acid (AA) metabolism *via* COX inhibition by either traditional NSAIDs or selective cyclooxygenase-2 (COX-2) inhibitors could lead to the generation of pro-inflammatory leukotrienes and lipoxins *via* the LOX pathway, partly accounting for the side effects seen with traditional NSAIDs and selective COX-2 inhibitors. To counter this, several LOX phospholipase A_2 (PLA_2) inhibitors have been reported nowadays from natural sources (Sharanya et al. 2020). Avenanthramides from Oats (Landberg, Sunnerheim, and Dimberg 2020), some flavonoids from *Sophora flavescens*, and *Sideritis tragoriganum* (Werz 2007) have been reported for LOX inhibition activity. A flavonoid myricetin extracted from *Myrica nagi (1)* showed remarkable selective inhibition of the COX-2 enzyme with an IC_{50} value of 112 µg/mL (Kumar, et al. 2019). Likewise, Curcumin from *Curcuma longa (2)*, a polyphenolic β-diketone presented moderate COX-2 inhibition (IC_{50} value 30 µmol/L) but potential potent PG-E2 synthase 1 enzyme activity (IC_{50} value 0.3 µmol/L) (Koeberle, Northoff, and Werz 2009). A diterpenoid 6- hydroxy salvinolone extracted by RP-HPLC column chromatography from *Premna integrifolia (3)* exhibited nonselective COX2 and LOX inhibition with IC_{50} values of 6.15 µg/mL and 11.33 µg/mL, respectively (Azad et al. 2018). An aqueous extract of aerial parts of *Desmodium*

gangeticum (4) showed a moderate enzyme nonselective inhibition against COX2 and LOX with IC_{50} values of 39 µg/mL and 59 µg/mL, respectively (Bisht, Bhattacharya, and Jaliwala 2014). The overall mechanism for this above-discussed COX inhibition by *Myrica nagi, Curcuma lomga,* and *Desmodium gangeticum* is presented in Figure 7.

The solvent extractions followed by repeated chromatographic purification of the *Hosta plantaginea* flowers (traditional Chinese medicinal plants used to treat inflammatory and painful diseases with partial scientific validation) led to the isolation of one new flavonoid glycoside, hostaflavone A **(128),** together with one related known compound, kaempferol-3-O-sophoroside-7-O-glucoside **(129).** Compounds **128** and **129** were evaluated for anti-inflammatory activity against cyclooxygenases (COX-1 and COX-2) *in vitro*. The results revealed that 1 and 2 exhibited significant COX-1 and moderate COX-2 inhibition compared to the reference celecoxib (He et al. 2019). A new flavan-3-ol glycoside, hostaflavanol A (**130**), along with two related known ones, including dihydrokaempferol (**131**) and naringenin (**132**), was isolated by silica gel and ODS column chromatography from the 80% ethanol extract of *Hosta plantaginea* flowers. The anti-inflammatory activity of these compounds against cyclooxygenases (COX-1 and COX-2) *in vitro* results revealed that compounds 144 exhibited significant or moderate COX-1 and moderate COX-2 inhibitory effects with IC_{50} values of 23.7, 31.6, and 61.3 µM for COX-1, as well as 46.7, 71.2, and 115.7 µM for COX-2, respectively (Yang et al. 2020). Compounds **133–136**, namely plantanone A **(133),** plantanone B **(134),** kaempferol-

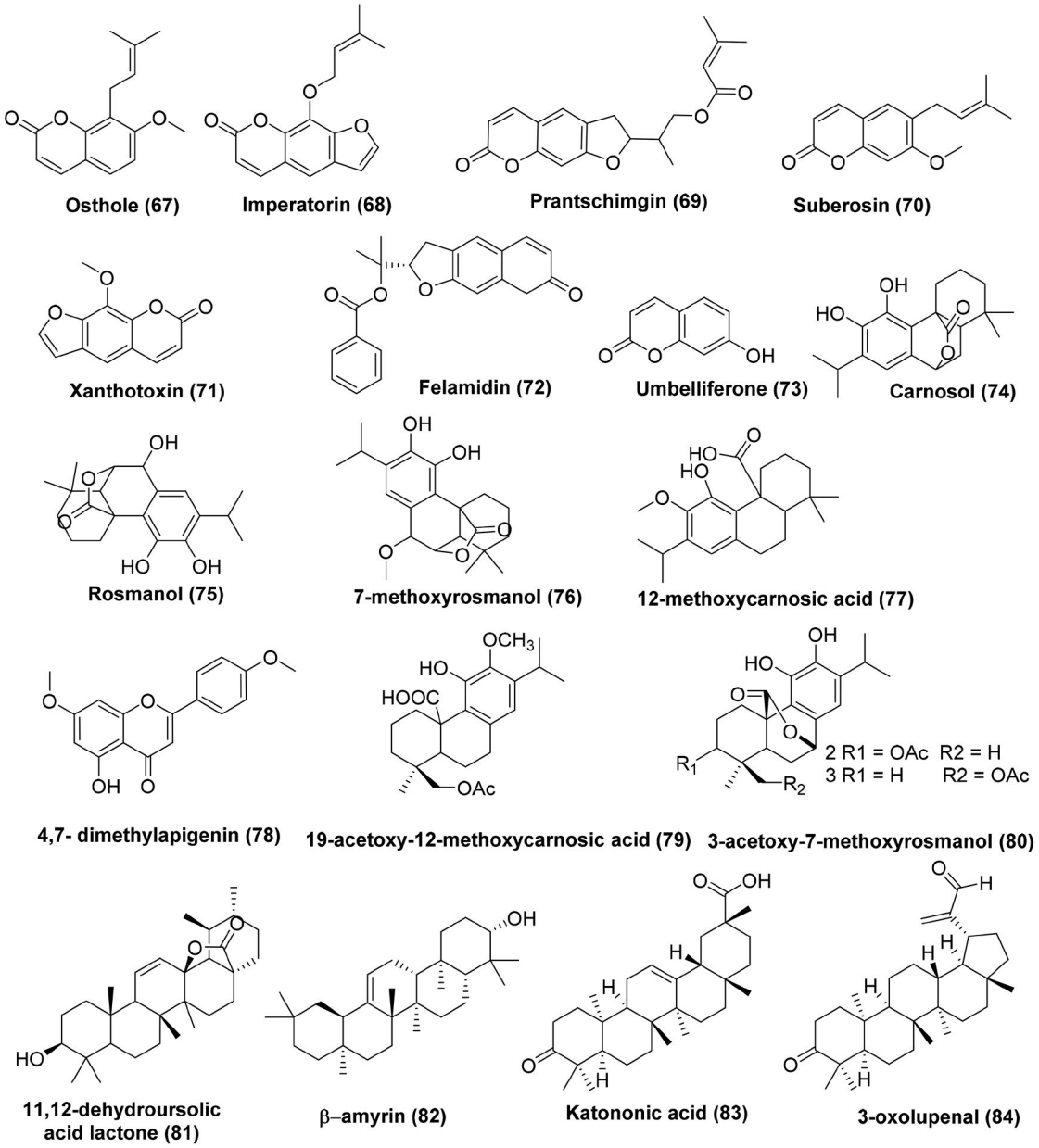

Figure 7. Potential role of plant-based enzyme inhibitors in the arachidonic acid inflammatory Pathway. (Arachidonic acid (A), the major polyunsaturated fatty acid (PUFA) present in mammalian systems, is oxygenated by cyclooxygenase (COX), the lipoxygenase (LOX) to produce inflammatory mediators that are upregulated in various pathological conditions esp. Rheumatoid arthritis, Osteoarthritis and Cancer).

3-*O*-b-D-glucopyranosyl-(1/2)-[a-L-rhamnopyranosyl-(1/6)]-b-D-glucopyranoside (4) **(135),** and kaempferol-3-*O*-(2G-glucosylrutinoside)-7- *O*-glucoside **(136),** were isolated (by utilizing silica gel, Spehadex-LH 20, and semi-preparative HPLC techniques), from the flowers of *Hosta plantaginea*. Further detailed testing showed that compounds **134-136** inhibited the COX-1 and COX-2 enzymes with IC_{50} values of 12.90–33.37 µM and 38.32–46.16 µM, respectively. Our results suggested that the anti-inflammatory and antioxidant activities of *H. plantaginea* flowers are partly attributed to these flavonoids (He et al. 2018). Geranyl flavones have been studied as compounds that potentially can be developed as anti-inflammatory agents. A series of natural geranylated flavanones including 3′,4′-*O*-dimethyl-5′-hydroxydiplacone **(137)**, mimulone **(138),** diplacone **(139),** 3′-O-methyl-5′-hydroxydiplacone **(140),** tomentodiplacone O **(141),** tomentone **(142),** 3′-O-methyl-5′-methoxydiplacone **(143),** geranylchromone **(144),** and paulownione C **(145)**, were isolated (by column chromatography and semipreparative RP-HPLC) from *Paulownia tomentosa* fruits. These compounds were studied for their anti-inflammatory activity to inhibit cyclooxygenases (COX-1 and COX-2) and 5-lipoxygenase (5-LOX) and their possible mechanism of action. The compounds tested **(137–145)** showed variable degrees of activity, with several showing activity comparable to or greater than the standards used in COX-1, COX-2, and 5-LOX assays. However, only the compound tomentodiplacone O **(141)** showed more selectivity against COX-2 versus COX-1 when compared with ibuprofen. The ability of the test compounds to interact with the enzymes mentioned above was supported by docking studies (Hanáková et al. 2017). The COX-2 inhibition activity of compounds verbascoside **(146)** and 6′-*O*-acetylverbascoside **(147)** isolated from the roots of *Tecoma mollis* was evaluated. Compounds **146** and **147** showed promising COX-2 inhibitory action, IC_{50} values of 11.3 µM, and 9.4 µM respectively (Abdel-Mageed et al. 2017). Aloe emodin **(150),** identified from ethyl acetate extract of *Cassia angustifolia* showed promising LOX inhibition with an IC_{50} of 29.49 µM (Sharanya et al. 2020). Phytochemical study on rhizomes of *Cimicifuga dahurica* resulted in the isolation of cimicifugic acid A **(151)** (by using HP-20 resin column chromatography, ODS CC, and preparative HPLC) and evaluated for anti-inflammatory potentials against COX-2 and PGE_2 production and the tested compound showed moderate anti-inflammatory activities (Lu et al. 2019). A compound, quercetin-3-methoxy-4′-glucosyl-7-glucoside **(152),** isolated by silica gel column chromatography from *Melothria heterophylla* was evaluated for anti-inflammatory activity against cyclooxygenase-1 (COX-1)- and COX-2 enzymes. The test compound **152** was found to inhibit COX-1 (IC_{50} 2.76 µg/mL) and, more efficiently, COX-2 (IC_{50} 1.99 µg/mL) (Mondal, Maity, and Bishayee 2019). In this study, isolated flavonoids from several *Artocarpus* species, artocarpin **(153)**, isobavachalcone **(154)**, 2′,4′-dihydroxy-4-methoxy-3′-prenyldihydrochalcone **(155)**, 4′,5- dihydroxy-6,7-(2,2-dimethylpyrano)-2′-methoxy-8-γ,γ –dimethylallylflavone **(156)**, artonin E **(157)** and oxyresveratrol **(158)** were investigated for their inhibitory effects on the production of prostaglandin E2 (PGE2) in human plasma. Compounds **153**, **155**, **157**, and **158** were the most potent inhibitor in inhibiting the biosynthesis of PGE2 with IC_{50} value of 11.66 µM, 8.99 µM, 7.04 µM, and 8.98 µM, respectively. Different substitution pattern of the flavonoids may contribute to different range of inhibitory activity (Sazali et al., 2017). A new flavonol derivative: cyperaflavoside (myricetin 3,3′,5′-trimethyl ether 7-*O*-β-D-glucopyranoside) **(159)** and five flavonoids: vitexin **(160)**, orientin **(161)**, cinaroside **(162)**, quercetin 3-*O*-β-D-glucopyranoside **(163)**, and myrcetin 3-*O*-β-D-glucopyranoside **(164)** were separated by sephadex LH-20 column chromatography from the methanolic extract of *Cyperus rotundus* aerial parts were assessed for their 5-lipoxygenase inhibitory potential. All compounds possessed 5-lipoxygenase inhibitory potentials with IC_{50} values of 5.1, 4.5, 5.9, 4.0, 3.7, and 2.3 µM, respectively, in comparison to indomethacin (IC_{50} 0.98 µM). These results supported the traditional uses of *C. rotundus* in treating inflammation and its related symptoms (Ibrahim et al. 2018). The chemical structures of different secondary metabolites as enzyme inhibitors linked to inflammation are presented in Table 6 and Figure 8. The isolation and assessment of various natural substances for their anti-inflammatory effects on the cyclooxygenases (COX-1 and COX-2) and 5-lipoxygenase (5-LOX) enzymes have been described. *Hosta plantaginea* flowers, *Paulownia tomentosa* fruits, *Tecoma mollis* roots, *Cassia angustifolia*, *Cimicifuga dahurica* rhizomes, and *Melothria heterophylla* were among the plants from which the chemicals were extracted. The findings indicate that these natural substances have the potential to be developed as anti-inflammatory medicines and also demonstrated moderate to strong anti-inflammatory properties.

Tyrosinase inhibition

Tyrosinase is a copper-containing polyphenol oxidase, which leads to the conversion of that $_L$-tyrosine to dopachrome, which is associated with the production of melanin, which helps in protection from ultraviolet rays. However, its overproduction culminates in skin problems and neurodegenerative disorders (Zengin et al. 2015; Zengin, Locatelli, et al. 2016). It is the key enzyme responsible for the biosynthesis of melanin, and its inhibition is considered the best strategy for treating epidermal hyperpigmentation problems (Sun et al. 2017). The overproduction of melanin because of the overactivity of tyrosinase can cause skin hyperpigmentation. Consequently, natural bioactive compounds modulating pigmentation metabolism have shown significant importance (Baurin et al. 2002; Mapunya et al. 2011). In humans, tyrosinase inhibitors help treat hyperpigmentation like nevus, lentigo, and post-inflammatory stages (Parvez et al. 2006). Kojic acid and arbutin are common tyrosinase inhibitors, but they adversely affect human health (Chen et al. 2015). Tyrosinase inhibitors are active agents that can reduce enzymatic reactions such as food browning and hyperpigmentation of human skin (Zengin et al. 2017). Flavonoids have

Table 6. Secondary metabolites as enzyme inhibitors linked to inflammation.

Compounds	Source	COX-1	COX-2	LOX	PGE2 synthase
Hostaflavone A **(128)**	*Hosta plantaginea*	35.2 [a]	41.9 [a]	–	–
Kaempferol-3-O-sophoroside-7-O-glucoside **(129)**	*Hosta plantaginea*	37.2 [a]	40.2 [a]	–	–
Hostaflavanol A **(130)**	*Hosta plantaginea*	23.7 [a]	46.7 [a]	–	–
Dihydrokaempferol **(131)**	*Hosta plantaginea*	31.6 [a]	71.2 [a]	–	–
Naringnin **(132)**	*Hosta plantaginea*	61.3 [a]	115.7 [a]	–	–
Plantanone A **(133)**	*Hosta plantaginea*	33.37 [a]	46.16 [a]	–	–
Plantanone B **(134)**	*Hosta plantaginea*	21.78 [a]	44.01 [a]	–	–
kaempferol-3-O-b-D-glucopyranosyl-(1/2)-[a-L-rhamnopyranosyl-(1/6)]-b-D-glucopyranoside (4) **(135)**	*Hosta plantaginea*	12.90 [a]	45.21 [a]	–	–
kaempferol-3-O-(2G-glucosylrutinoside)-7-O-glucoside **(136)**	*Hosta plantaginea*	20.74 [a]	38.32 [a]	–	–
3′,4′-*O*-dimethyl-5′-hydroxydiplacone **(137)**	*Paulownia tomentosa*	6.4 [a]	4.2 [a]	–	–
Mimulone **(138)**	*Paulownia tomentosa*	6.0 [a]	3.7 [a]	0.05 [a]	–
Diplacone **(139)**	*Paulownia tomentosa*	1.8 [a]	4.2 [a]	0.06 [a]	–
3′-O-methyl-5′-hydroxydiplacone **(140)**	*Paulownia tomentosa*	3.3 [a]	10.6 [a]	–	–
Tomentodiplacone O **(141)**	*Paulownia tomentosa*	26.3 [a]	9.5 [a]	–	–
Tomentone **(142)**	*Paulownia tomentosa*	–	–	0.35 [a]	–
3′-O-methyl-5′- methoxydiplacone **(143)**	*Paulownia tomentosa*	–	–	0.38 [a]	–
Geranylchromone **(144)**	*Paulownia tomentosa*	–	–	2.46 [a]	–
Paulownione C **(145)**	*Paulownia tomentosa*	–	–	0.37 [a]	–
Verbascoside **(146)**	*Tecoma mollis*	–	11.3 [a]	–	–
6′-*O*-acetylverbascoside **(147)**	*Tecoma mollis*	–	9.4 [a]	–	–
Isoverbascoside **(149)**	*Tecoma mollis*	–	13.4 [a]	–	–
Aloe emodin **(150)**	*Cassia angustifolia*	–	–	29.49 [a]	–
Cimicifugic acid D **(148)**	*Cimicifuga dahurica*	–	70.15 [a]	–	70.15 [a]
Cimicifugic acid A **(151)**	*Cimicifuga dahurica*	–	27.42 [a]	–	27.4 [a]
Quercetin-3-methoxy-4′-glucosyl-7-glucoside **(152)**	*Melothria heterophylla*	2.76 [b]	1.99 [b]	–	–
Artocarpin **(153)**	*Artocarpus* species	–	–	–	11.66 [a]
Isobavachalcone **(154)**	*Artocarpus* species	–	–	–	16.55 [a]
2′,4′-dihydroxy-4-methoxy-3′-prenyldihydrochalcone **(155)**	*Artocarpus* species	–	–	–	8.99 [a]
4′,5- dihydroxy-6,7-(2,2-dimethylpyrano)-2′-methoxy-8-γ,γ –dimethylallylflavone **(156)**	*Artocarpus* species	–	–	–	7.04 [a]
Artonin E **(157)**	*Artocarpus* species	–	–	–	8.98 [a]
Oxyresveratrol **(158)**	*Artocarpus* species	–	–	–	25.18 [a]
Cyperaflavoside **(159)**	*Cyperus rotundus*	–	–	5.1[a]	–
Vitexin **(160)**	*Cyperus rotundus*	–	–	4.5 [a]	–
Orientin **(161)**	*Cyperus rotundus*	–	–	5.9 [a]	–
Cinaroside **(162)**	*Cyperus rotundus*	–	–	4.0 [a]	–
Quercetin 3-*O*-β-D-glucopyranoside **(163)**	*Cyperus rotundus*	–	–	3.7 [a]	–
Myrcetin 3-*O*-β-D-glucopyranoside **(164)**	*Cyperus rotundus*	–	–	2.3 [a]	–

Abbreviations: a: μM; b: μg/mL.

been reported to act both as substrates and inhibitors against tyrosinase by precipitating the tyrosinase enzyme, thus inhibiting enzymatic activity (Pettersen et al. 2004). Similarly, the *Caragana sinica* has already been documented to inhibit tyrosinase *in vitro* (Jeon et al. 2012). The chemical structure of different secondary metabolites as enzyme inhibitors linked to skin problems is shown in Figure 9, and their list is presented in Table 7.

Quercetin identified from *Hypericum laricifolium* exhibited the most potent tyrosinase inhibition (IC_{50}:14.29 μM) (Quispe et al. 2017). To find a natural compound with inhibitory activity toward tyrosinase, the five flavonoids of kushenol A **(165)**, 8-prenylkaempferol **(166)**, kushenol C **(167)**, formononetin **(168)** were isolated by column chromatography from a 95% methanol extract of *Sophora flavescens*. The ability of these flavonoids to block the conversion of L-tyrosine to L-DOPA by tyrosinase was tested *in vitro*. Compounds **166** and **167** exhibited potent inhibitory activity, with IC_{50} values less than 10 μM. Furthermore, enzyme kinetics and molecular docking analysis revealed the formation of a binary encounter complex between compounds 1-4 and the enzyme (Kim, Cho, et al. 2018). Glabridin **(169),** an isoflavan, isolated from the root of *Glycyrrhiza glabra* Linn, has exhibited several pharmacological activities, including excellent inhibitory effects on tyrosinase. In another paper, the inhibitory kinetics of glabridin on tyrosinase and their binding mechanisms were determined using a spectroscopic, zebrafish model, and molecular docking techniques. The results indicate that glabridin reversibly inhibits tyrosinase noncompetitively through a multiphase kinetic process with the IC_{50} of 0.43 μmol/L (Chen, Yu, and Huang 2016). Phloretin-4-*O*-β-D-glucopyranoside (**170**), isolated from *Homalium stenophyllum* (Sephadex LH-20, RP-18 column chromatography and semipreparative HPLC), was tested for its anti-tyrosinase inhibition potential (Shimakage and Nihei 2022). Lupinalbin **(171),** isolated by column chromatography from the tubers of *Apios americana* showed tyrosinase

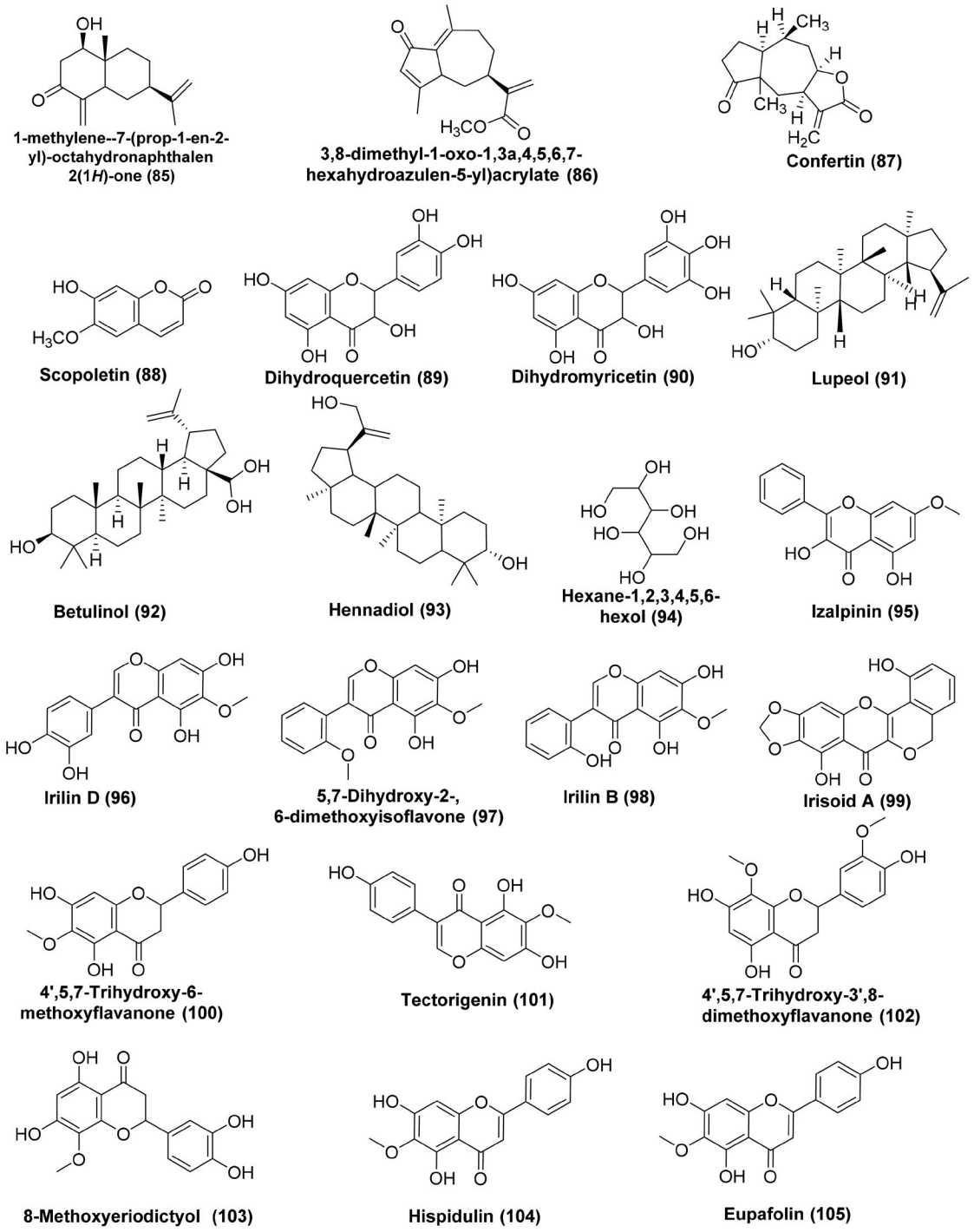

Figure 8. Secondary metabolites as enzyme inhibitors linked to inflammation.

inhibition potential (Kim, Cho, et al. 2018). The compounds namely 2(*S*) isobutanol 2-O-β-D-arabinopyranosyl (1→6)-O-β-D-glucopyranoside **(173),** *Z*)-3-hexenyl-O-β-D-glucopyranoside **(174),** ′-O-benzyl-α-L-rhamnopyranosyl-(1″→6′)-β-D-glucopyranoside **(175),** 2-phenylethyl-O-β-D-glucopyranoside **(177),** guaiacylglycerol **(176),** guaiacylglycerol 8-O-β-D-glucopyranoside **(178),** and Xylocoside B [1-hydroxy-3-(4-hydroxy-3,5-dimethoxyphenyl)prop-2-yl β glucopyranoside] **(179)** isolated (by silica gel column chromatography) from *Piper aduncum* leaves were studied for tyrosinase inhibition. The results showed that compounds **174**, **178**, and **179** exhibited significant tyrosinase inhibitory activity with IC_{50} values of 39.3, 41.3, and 37.5 µM, respectively. Compounds **173**, **175**, **177**, and **176** showed moderate inhibitory activity, with IC_{50} values of 76.3, 80.1, 63.4, and 51.1 µM, respectively (Luyen et al. 2017). Six compounds, including sanggenon M **(180),** chalcomoracin **(181),** sorocein H **(182),** kuwanon J **(183)**, sanggenon C **(184),** and sanggenon O **(186)** isolated by using silica gel and spehadex LH-20 column chromatography from the twigs of *Morus nigra* were evaluated for tyrosinase inhibition potential (Hu et al. 2018). The twigs of *Morus alba* were found to show

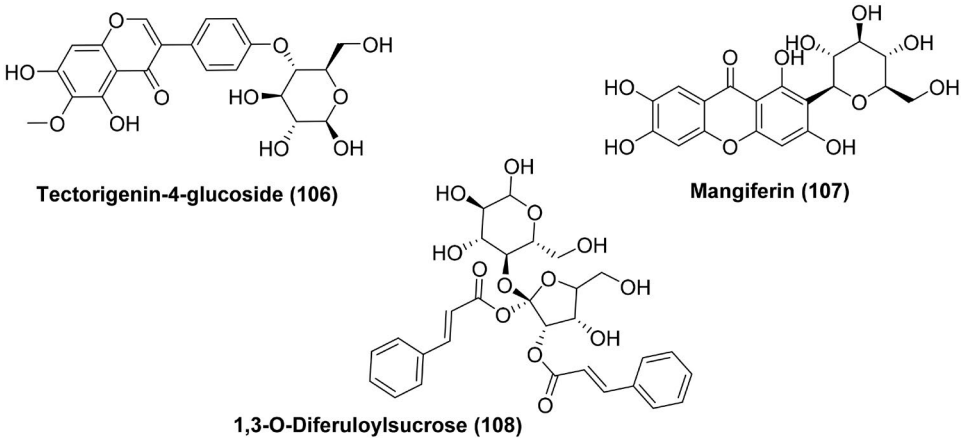

Figure 9. Secondary metabolites as enzyme inhibitors linked to skin problems.

Table 7. Secondary metabolites as enzyme inhibitors linked to skin problems.

Active constituent	Source	TYR
Quercetin **(50)**	*Hypericum laricifolium*	14.29 [a]
Kushenol A **(16)**	*Sophora flavescens*	1.1 [a]
8-prenylkaempferol **(166)**	*Sophora flavescens*	2.4 [a]
Kushenol C **(167)**	*Sophora flavescens*	24.1 [a]
Formononetin **(168)**	*Sophora flavescens*	19.9 [a]
Glabridin **(169)**	*Glycyrrhiza glabra*	0.43[b]
Phloretin-4-O-β-D-glucopyranoside **(170)**	*Homalium stenophyllum*	741 [a]
Lupinalbin **(171)**	*Apios americana*	39.7 [a]
2′-hydroxygenistein-7-O-gentibioside **(172)**	*Apios americana*	50.0 [a]
2(*S*) isobutanol 2-O-β-D-arabinopyranosyl (1→6)-O-β-D-glucopyranoside **(173)**	*Piper aduncum*	76.3 [a]
Z)-3-hexenyl-O-β-D-glucopyranoside **(174)**	*Piper aduncum*	39.3 [a]
′-O-benzyl-α-L-rhamnopyranosyl-(1″→6′)-β-D-glucopyranoside **(175)**	*Piper aduncum*	80.1 [a]
2-phenylethyl-O-β-D-glucopyranoside **(177)**	*Piper aduncum*	63.4 [a]
Guaiacylglycerol **(176)**	*Piper aduncum*	51.1 [a]
Guaiacylglycerol 8-O-β-D-glucopyranoside **(178)**	*Piper aduncum*	41.3 [a]
Xylocoside B [1-hydroxy-3-(4-hydroxy-3,5-dimethoxyphenyl)prop-2-yl β glucopyranoside] **(179)**	*Piper aduncum*	37.5 [a]
Sanggenon M **(180)**	*Morus nigra*	13.06 [a]
Chalcomoracin **(181)**	*Morus nigra*	2.59 [a]
Sorocein H **(182)**	*Morus nigra*	6.49 [a]
Kuwanon J **(183)**	*Morus nigra*	0.17 [a]
Sanggenon C **(184)**	*Morus nigra*	1.1.7 [a]
Sanggenon O **(186)**	*Morus nigra*	1.15 [a]
Steppogenin **(185)**	*Morus alba*	0.98 [a]
2,4,2′,4′-tetrahydroxychalcone **(187)**	*Morus alba*	0.07 [a]
Morachalcone A **(188)**	*Morus alba*	0.08 [a]
Oxyresveratrol	*Morus alba*	0.10 [a]
Moracin M **(189)**	*Morus alba*	8.00 [a]
6-hydroxy-7-methoxy-2-[2-(3-hydroxy-4-methoxyphenyl)ethyl]chromone **(190)**	*Aquilaria*	89.0 [a]
6,8-dihydroxy-2-[2-(4-methoxyphenyl)ethyl]chromone **(191)**	*Aquilaria*	51.5 [a]

Abbreviations: a: uM; b: μmol/L.

intense tyrosinase inhibition activity. The responsible active extract on isolation by silica gel and Sephadex LH-20 column chromatography led to the identification of steppogenin **(185)**, 2,4,2′,4′-tetrahydroxychalcone **(187)**, morachalcone A **(188)**, oxyresveratrol, and moracin M **(189)** with tyrosinase inhibition potential. The compounds **185** (IC_{50} 0.98 μM), **187** (IC_{50} 0.07 μM), **188** (IC_{50} 0.08), and **189** (IC_{50} 8.00 μM) exhibited significant tyrosinase inhibition activities, much stronger than that of the positive control kojic acid. These results suggest that *M. alba* twig extract should serve as a good source of natural tyrosinase inhibitors for use in foods as antibrowning agents or in cosmetics as skin-whitening agents (Zhang, Zhang, et al. 2016). The ethyl ether extract of agarwood from an *Aquilaria* plant afforded the isolation of 6-hydroxy-7-methoxy-2-[2-(3-hydroxy-4-methoxyphenyl)ethyl]chromone **(190)** and 6,8-dihydroxy-2-[2-(4-methoxyphenyl)ethyl]chromone **(191)** by silica gel and semi-preparative HPLC techniques. The compounds **190** and **191** exhibited tyrosinase inhibitory effects with IC_{50} values of 89.0 and 51.5 μM, respectively (Yang et al. 2019). Overall, tyrosinase, an enzyme involved in the production of melanin and a potential contributor to skin hyperpigmentation, is discussed in relation to its suppression. Natural bioactive substances found as tyrosinase inhibitors, such as flavonoids and glabridin, are being researched for their possible application in treating hyperpigmented skin issues. The chemical substances quercetin, kushenol A, glabridin, phloretin-4-O-D-glucopyranoside, lupinalbin, and 2′-hydroxygenistein-7-O-gentibioside have all been found as tyrosinase inhibitors.

3. Conclusion and future aspects

The utilization of food plants for their varied health advantages and future medicinal uses has recently seen a blossoming in the scientific literature, particularly in nutritional sciences. Although growth in the pharmaceutical field and dramatic expansion in the knowledge of organic chemistry deeply embedded the preference for synthetic medications, yet, its negative side picture is more insecure in terms of its related side effects and high cost, which renewed the attraction of investigators toward natural products from various sources for drug. In conclusion, medicinal plants and derived natural products from plants have potential enzyme inhibitors. This is confirmed by the fact that hundreds of new natural inhibitors derived from the natural world and able to target important biological human proteins or enzymes are identified and characterized every year. Some of these molecules have been considered promising therapeutic molecules in the last decades because of their high selectivity or potency. They have been included in clinical trials to evaluate their effectiveness. Enzyme inhibitors play a significant role in the drug discovery process. Understanding diseases at the molecular level has revealed the root cause is the dysfunction, overexpression, or hyperactivation of the enzymes involved. This hyperactivation or overexpression of enzymes can be treated by using suitable enzyme inhibitors. These efforts have provided several enzyme inhibitors in clinics. The presence of appropriate levels of enzymes is crucial in maintaining a healthy body system. However, overexpression of enzymes may lead to an abnormal cascade of biological events, ultimately resulting in disease. Even though several natural inhibitors in the medicinal plant kingdom exist, their use has a safety issue due to their associations with other undesired molecules that have not been fully elucidated. Therefore, even though medicinal plants have vast potential for curing and managing various diseases, the challenge remains to determine specific components of specific pharmacological activity and establish their safety. Most inhibitors interact with particular enzymes by blocking their activity toward their corresponding physiological natural substances without disturbing other enzymes. Among the secondary metabolites that were looked into, phenolics and flavonoids were the most effective enzyme inhibitors. The considerable antioxidant and anti-inflammatory effects of flavonoids were demonstrated in several investigations, indicating the therapeutic potential of these compounds. Many medicinal food plants, their crude extracts, fractions, and isolated compounds have been researched. Although several exciting compounds that are dependent on the enzyme have been discovered, it is advised that further research be conducted to develop potentially pharmacologically active functional foods.

This review will direct the researcher to isolate bioactive compounds from plants with excellent enzymatic action. Thus, exploring new, known, and novel enzyme inhibitors with progressive therapeutic potential and fewer side effects is required to treat diseases in humankind and animals. Further research is needed in the scientific community to explore the possible mechanisms behind these enzyme inhibitors that may be developed as new enzyme-inhibitory drugs shortly. The discovery of new natural products will also provide a new scaffold to synthetic chemistry for further development/optimization of new drug candidates. In conclusion, medicinal plants and natural compounds generated from plants can regulate enzyme activity. This in-depth review article will guide the researchers in the right direction to isolate bioactive chemicals from plants with outstanding enzymatic activity. To effectively cure diseases that affect both people and animals, it is necessary to conduct research into new enzyme inhibitors, as well as those already known to exist and utterly new enzyme inhibitors. The scientific community needs to do further study to investigate the potential processes behind these enzyme inhibitors, which might lead to the creation of novel enzyme-inhibitory medications in the future. The finding of novel natural products will also give a new scaffold to synthetic chemistry, which may then be used to develop and optimize potential new therapeutic candidates. Because of this, future research needs to concentrate on elucidating the processes underlying these enzyme inhibitors and generating novel pharmaceuticals based on them. In addition, the discovery of new natural products can serve as a basis for the further development and optimization of potential new medication candidates.

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