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Pharmacologically Active Secondary Metabolites from *Psoralea corylifolia*

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Abstract

Psoralea corylifolia has gained much attention, particularly in the cosmetic industry for the past few years owing to promising pharmacological activities of its metabolites. Seeds of *P. corylifolia* are the main source of bakuchiol, a meroterpene compound that is extensively harnessed in numerous skincare products. Furanocoumarins, psoralen and isopsoralen are other metabolites mainly from *P. corylifolia* seeds and known for their antipsoriatic activity. Moreover, various studies have reported several classes of secondary metabolites from this plant possessing diverse biological activities. This article highlights recent updates on *P. corylifolia* phytoconstituents and their promising pharmacological activities mainly on skin-related diseases as well as for the treatment of degenerative diseases based on scientific publications during the last 10 years (2011-2021). The literature search was carried out through scientific-based websites and databases such as Google Scholar, NCBI, and PubMed. This paper included sixty-three bioactive metabolites belonging to the group of flavonoids, meroterpenes, furanocoumarins, coumestans, steroid and phenolic compounds. A broad range of bioactivities of these phytoconstituents including skin disease management, antibacterial, anti-inflammatory, hepatoprotective, antidiabetic, controlling obesity, estrogenic, osteoporosis management, and cytotoxicity are described in this review.

Keywords: Bakuchiol, pharmacological activities, Psoralea corylifolia, bioactive metabolites

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1 Introduction

The genus Psoralea is predominantly found in different regions of the southern part of Africa, Asia, Australia, and North America. This genus is an indigenous plant of tropical and subtropical, which is first established by Linnaeus in 1742. Many species of Psoralea are endemic to the Greater Cape Floristic Region (GCFR) of South Africa which is also become the center of their diversity [1]. However, *Psoralea corylifolia* species mainly grows in Asia, mostly in China, India and Southeast Asia [2]–[4].

Psoralea corylifolia (syn. *Cullen corylifolium*) belongs to Fabaceae family, a popular herb in various traditional medicine systems [5]. The plant is called *Bu Gu Zhi* in China [6], *Boh-Gol-Zhee* in Korea [7], *Bakuchi* in India [8] and is known as *Babchi* in other countries. It is commonly used in both Indian and Chinese traditional medicines. In Traditional Chinese Medicine (TCM), dried fruits of *P. corylifolia* were recorded to treat andrological disorders and possess the ability to strengthen kidney Yang in TCM theory. In an ancient Rihuazi's Chinese Materia Medica (618-907 AC), fruits of *P. corylifolia* were mentioned to possess an aphrodisiac effect and could improve the activity of the male reproductive system. In Kai Bao Ben Cao or Materia Medica of Kai Bao (973-974 AC), fruits of *P. corylifolia* were used to cure spermatorrhea caused by the deficiency of kidney Yang [9]. Furthermore, seeds of *P. corylifolia* were used in Ayurvedic system in India to treat various pathological conditions, such as skin disorders including psoriasis, leucoderma, leprosy, and also used for its stimulant, diuretic, laxative, anthelmintic, and diaphoretic effects [10], [11].

Morphologically, *P. corylifolia* is an erect herbaceous plant with various heights ranging from 0.6 to 1.2 m. It has a grooved stem and its leaves are broadly elliptical and hairy. The flowers are blue, solitary, and dense in the axillary with 10–30 flowered racemes. The plant has 5 mm long black fruits with ovoid-oblong to mucronate shape. Seeds are oblong flattened with dark brown color and have an aromatic odor [12].

In 1933, the first naturally occurring furanocoumarin called psoralen was reported from fruits of *P. corylifolia* [13]. Subsequently, other important furanocoumarin derivatives were isolated from this plant, including isopsoralen and psoralidin, as well as a meroterpenoid phenol, bakuchiol (Figure 1). These compounds are known as major bioactive constituents of *P. corylifolia*, possessing a broad range of pharmacological activities. To date, psoralen and isopsoralen are clinically used to cure numerous skin diseases, such as psoriasis, eczema, and vitiligo [14]. A series of studies on psoralen and isopsoralen also revealed their biological activities as antibacterial [15], antidepressant-like effect [16], anti-osteoporotic [17], anti-inflammatory [18], and antitumor [19].

Bakuchiol is another important metabolite produced by P. *corylifolia*. This compound is widely used in cosmetic products owing to its antimicrobial, anti-inflammatory, antioxidant, and anti-aging properties. Bakuchiol has also been proposed as a natural substitute for retinol to treat several skin conditions such as skin hyperpigmentation, wrinkles, and acne care in cosmetic applications. Moreover, bakuchiol showed estrogenic, anticancer, hepatoprotective, cardioprotective, and hypoglycemic effects. The importance of bakuchiol especially for cosmetic applications led to increasing attention to *P. corylifolia* which is known as the only natural and valuable source for bakuchiol on a large scale [20]. The present review intents to provide current updates on research findings regarding phytoconstituents and biological activities of *P. corylifolia* metabolites, which might open new insights to further therapeutic application of its promising secondary metabolites.

2 Experimental section

This article is written through literature reviews from international journals that have been published in the last 10 years (2011-2021). Only original research articles were included for this review. Data search was carried out through scientific-based websites and databases (Google Scholar, NCBI, and PubMed) using the following keywords: "*Psoralea corylifolia*", "*Pharmacological*

activity", "*Bakuchi", Babchi*", "*Bakuchi bioactivities*" and "*Phytochemical*".

3 Results and Discussion

During the last 10 years (2011-2021), 63 bioactive compounds were reported in research papers on *P. corylifolia,* many of which have been previously described beyond 2011. These compounds can be classified into flavonoids, steroid, meroterpenes, furanocoumarins, and coumestans, as listed in Table 1. Pharmacological studies on these compounds revealed their promising activities as antipsoriatic, anti-inflammatory, antibacterial, antidiabetic, antihiperlipidemia, hepatoprotective, estrogenic, osteoporosis management and cytotoxicity.

Table 1. Compounds identified from different parts of *P. corylifolia* and their promising bioactivities

Parts of plant	Class of metabolite	Compounds	Bioactivity	References
Fruits	Steroid	ß-sitosterol	Anti-inflammatory	[21]
Fruits	Flavonoid	Bavachalcone	Improving cognitive deficits, estrogenic	[22], [23]
		Isobavachalcone	Improving cognitive deficits, vasoactive, anti-neuroinflammatory, neuroprotective, inducing cell proliferation and apoptosis in colorectal cancer, hepatoprotective, anti-osteoporosis	[22], [24]–[28]
		Bavachin, Bavachinin	Improving cognitive deficits, vasoactive, estrogenic, DGAT inhibitor, anti-osteoporosis, PPAR-γ agonist	[6], [22]–[24], [28], [29]
		Neobavaisoflavone	Improving cognitive deficits, anti-neuroinflammatory, neuroprotective, estrogenic, hepatoprotective, anti-osteoporosis, PPAR-γ agonist, DGAT inhibitor	[6], [22], [23], [25], [27], [28]
		Corylin	Improving cognitive deficits, vasoactive, osteogenic, estrogenic, PPAR-γ agonist	[6], [22]–[24], [28], [30], [31]
		Bavachinone A	DGAT and α-glucosidase inhibitor, anti-osteoporosis, antibacterial, DGAT inhibitor	[3], [29]
		Bavachinone B	Antibacterial	[3]
		Hydroxypsoralenol A, B	DGAT and α-glucoside inhibitor	[30]
		Corylifol C	Radioprotective	[32]
Fruits	Flavonoid	7-O-Isoprenylcorylifol A,	Anti-inflammatory	[21]
Fruits	Coumestan	Bavacoumestan B	Antibacterial	[3]
Fruits	Meroterpene	12,13-dihydro-12,13-Epoxybakuchiol	Anti-inflammatory	[21]
		Corypsoriols A-N	Cytotoxic	[33]
Fruits	Meroterpene-flavane	Psocorylin F-Q	Cytotoxic	[33]
Seed	Furanocoumarin	8-Methoxypsoralen (8-MOP)	Antipsoriatic	[34]
		Isopsoralen	Antipsoriatic, vasoactive, reducing glucose-induced mesangial cell death, hepatoprotective, anti-neuroinflammatory, radioprotective	[24], [25], [27], [32], [34], [35]
		Bakuchicin	Antivasorelaxant, antibacterial, antitumor, CYP1A1 and CYP1A2 inhibitor in human liver microsomes	[36], [37]
Seed, fruit	Furanocoumarin	Psoralen	Antipsoriatic, Anti-inflammatory, vasoactive, anti-neuroinflammatory, neuroprotective, hepatoprotective, DGAT and α-glucosidase inhibitor, radioprotective	[21], [24], [25], [27], [30], [32], [34]
Seed, fruit	Coumestrols	Psoralidin	Antipsoriatic, preventing age-related cognitive deficits, vasoactive, anti-neuroinflammatory, neuroprotective, anticancer	[22], [24], [25], [34]
	Flavonoid	Corylifol A	Preventing age-related cognitive deficits alterations, myogenic activity, radioprotective, PPAR-γ agonist, DGAT inhibitor	[6], [10], [22], [29], [32]
	Coumestan	Bavacoumestan C	Antibacterial, DGAT and ?-glucoside inhibitor, anti-diabetic	[3], [30], [38]
Seed	Coumestan	Bavacoumestan D	DGAT and ?-glucosidase inhibitor	[30]
Seed	Meroterpene	Bakuchiol	Antipsoriatic, vasoactive, quorum sensing inhibitor, anti-neuroinflammatory, neuroprotective, ameliorates sepsis-induced acute kidney injury, antioxidant, antibacterial, hepatoprotective, anticancer, radioprotective	[4], [24], [25], [27], [32], [34], [39]–[41]
		7β, 13β-Psoracorylifol B 7β, 8α-Psoracorylifol D	DGAT inhibitor	[42]
Seed	Flavonoid	Isobacachromene	Myogenic activity	[10]
		Isobavachin	Estrogenic, PPAR-γ agonist	[6], [23]
		Corylifol B	DGAT and α-glucosidase inhibitor	[30]

	3''-methoxy-bavacoumestan C, 6,7-furanbavachinone B, 3,4- furanbavachalcone, 4,5- furanbavachalcone A	DGAT inhibitor	[29]
	Brosimacutin E	DGAT inhibitor, PPAR-γ agonist	[6], [29]
	5,40-dihydroxy-6,7-furanbavachalcone, 1''-methoxy-6,7-furanflavanone	protein tyrosine phosphatase 1B (PTP1B) inhibitor	[43]
	(2S)-4'-hydroxyl-7-hydroxymethylene-6-(2'',3''-epoxy-3''-methylbutyl) flavanone	Anti-diabetic	[38]
	4'-O-methylbavachalcone	Estrogenic, PPAR-γ agonist	[6], [23]

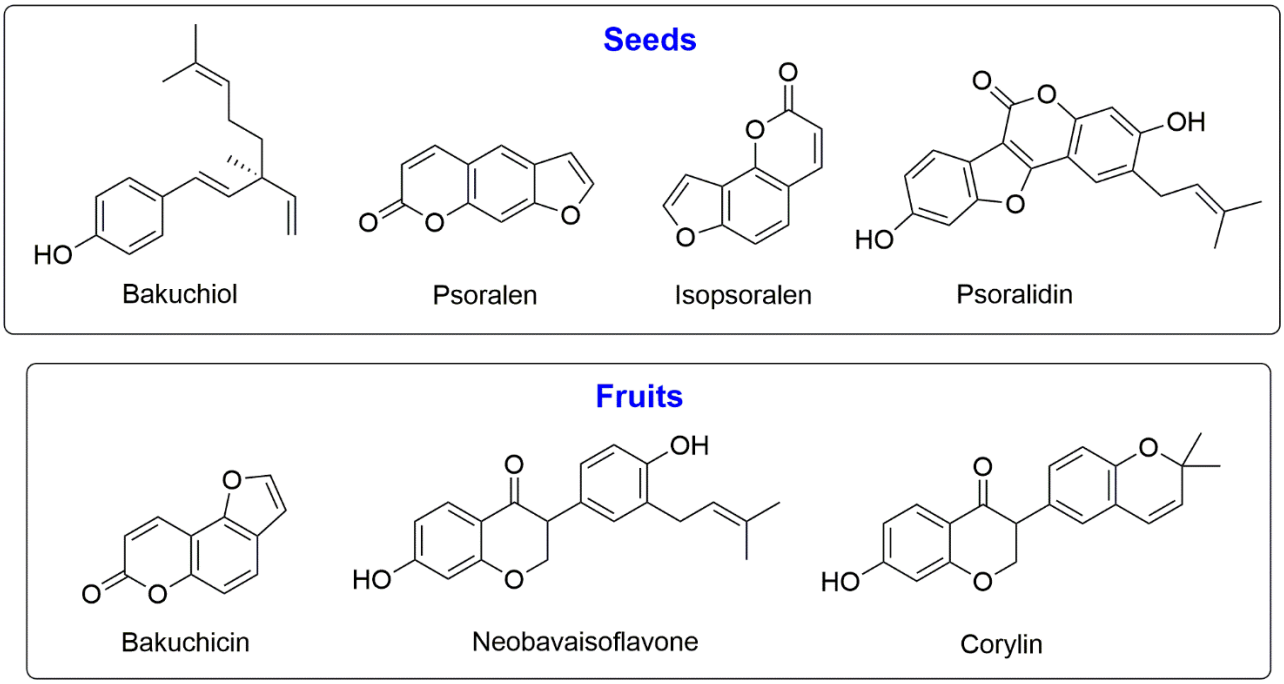

Figure 1. Structures of main bioactive metabolites from seeds and fruits of *P. corylifolia*

3.1 Skin Diseases Management

Seeds of *P. corylifolia* have been used to treat various skin diseases for centuries. In line with its traditional applications, several clinical studies also reported promising effects of formulations developed from seeds powder or natural products isolated from seeds or fruits of *P. corylifolia* to treat skin disorders such as vitiligo and skin inflammation [44]. A clinical study on the effect of a hydrophilic ointment containing 10% w/w of powder seeds of *P. corylifolia* to improve depigmentation in vitiligo disease was conducted in 2016. Vitiligo is a skin condition where white pale patches developed on the skin, due to damage of cutaneous melanocytes and affect the pigmentation of the skin. Various regimens to treat vitiligo have been developed but none of those can effectively cure the condition [45], [46]. This study included 20 healthy volunteers (18-60 years old) using a self-control trial. Volunteers were asked to apply the ointment on a selected white lesion once a day. During the study, 5 volunteers reported moderate irritation of which betamethasone was topically used as a counter-irritant, while the rest of the volunteers only experienced mild irritation. A few days after the first application of the ointment, the white patches became a bit red and normally pigmented skin grew from the edges of the lesions. In 12 weeks, the whole white lesions treated with the ointment were covered with the new pigment. The treatment was stopped and a follow-up observation was done up to 3 months after the trial was completed. No relapse was found and the volunteer's skin remained normal. This result showed that ointment containing 10% of *P. corylifolia* seeds

could be promising as a therapy for small white lessions of vitiligo [39].

Furthermore, a cream formulation containing 0.5% meroterpene phenol bakuchiol isolated from *P. corylifolia* seeds was found effective in improving facial photoaging, reducing wrinkles and hyperpigmentation with activities comparable to retinol, in a double-blind randomized clinical trial. The study was conducted for 12 weeks and 44 healthy participants were involved. Participants were randomly divided into 2 groups, each group received either facial cream containing 0.5% bakuchiol or 0.5% retinol [47]. Bakuchiol was reported before capable of inducing gene expression including those involved in cellular uptake and activation of retinol as well as controlling the production of extracellular matrix proteins, similar to that reported for retinol [48]. Moreover, bakuchiol enhanced cellular resistance to oxidative stress through activation of nuclear factor erythroid 2-related factor 2 (Nrf2) in addition to its capability as free radical scavenging [49]. Altogether these activities contribute to the antiaging effect of bakuchiol.

Further study on bakuchiol along with four other natural products isolated from *P. corylifolia* seeds namely psoralen, isopsoralen, 8-methoxypsoralen, and psoralidin, were carried out to uncover their potential activity against psoriasis-like lesions in the in vivo assay. 8-Methoxypsoralen is the most commonly used psoralens plus ultraviolet A (PUVA) therapy for the treatment of psoriasis so far. Among the tested compounds, isopsoralen, 8-methoxypsoralen and bakuchiol showed higher in vitro skin deposition in comparison to psoralen and psoralidin. Moreover, the combination of ultraviolet A (UVA) exposure and isopsoralen or 8-methoxypsoralen induced higher suppression in keratinocyte proliferation compared to other tested natural products, leading to better antipsoriatic potency of these furanocoumarins. Mechanistically, the action of isopsoralen and 8-methoxypsoralen in improving psoriasis-like lessions occurred through reduction of epidermal thickening, the release of cytokine, as well as skin barrier defects due to UVA therapy [34]. Eventually, this result indicated isopsoralen as a promising photosensitizing candidate for photochemotherapy against psoriasis-like lesions, along with the well-known 8-methoxypsoralen.

A recent study on a furanocoumarin derivative, bakuchicin, obtained from fruits of *P. corylifolia* showed its potency for the treatment of atopic dermatitis (AD) in AD-induced mice [50]. AD is a pruritic inflammatory skin disease that makes skin looks red and feels itchy [51]. Abnormalities in the immune system and exposure to allergens are known to contribute to this condition. AD is commonly treated with topical and oral corticosteroids, antihistamines, and immunosuppressants [52]. However, long-term therapy with those drugs could yield various side effects, which encourage research on natural products-based drug discovery and development as an alternative to treat atopic inflammation. In the study by Lim *et al*. (2020), thirty-five BALB/c mice (5 weeks old) were induced for an atopic dermatitis-like skin inflammation by applying 2,4-dinitrochlorobenzene (DNCB) and dermatophagoides farinae (house dust mite) extract onto mice ears. Treatment groups were orally administered with a series of doses of bakuchicin ranging from 0.1 to 10 mg/kg BW, while dexamethasone was used as a positive control. Administration of bakuchicin led to a significant decrease of ear thickness in a dose-dependent manner, in addition to decreasing epidermal and dermal thickness when compared to the negative control. At the molecular level, increasing T_h2 cytokines, pro-inflammatory cytokines, and pro-inflammatory chemokines were observed in AD-induced mice. Following the administration of bakuchicin, T_h2 gene expressions were down-regulated, leading to the suppression of pro-inflammatory cytokines and chemokines, the main inflammatory mediators contributing to the attenuation of AD symptoms [50].

3.2 Antibacterial Activities

Extract and phytoconstituents from fruits and seeds of *P. corylifolia* also showed promising antibacterial activity. A new flavonoid bavachinone B, together with bavacoumestans B and C from dried fruits of *P. corylifolia* were exerted moderate inhibition against *Staphylococcus mutans*-derived Sortase A [3]. Moreover, ethanol extract from seeds of *P. corylifolia* was found active against methicillin-resistant strain of *Staphylococcus aureus*

(MRSA) and *Listeria monocytogenes* with MIC values of 100 and 50 µg/mL, respectively. Further time-kill analysis indicated that complete inhibition of MRSA was achieved after 14 h exposure to the extract, while complete inhibition of *L. monocytogenes* was observed after 4 h of treatment. Damage in cell membrane integrity and changes in cellular membrane permeability of these bacteria were also detected upon treatment with extract [53], indicating the potential of *P. corylifolia* metabolites for further investigation on its antibacterial properties.

Methanol extract of *P. corylifolia* seeds and its main constituent, bakuchiol, also showed potency as a quorum sensing inhibitor (QSI) [11]. Quorum sensing (QS) is a signaling mechanism among bacterial cells allowing them to respond to population density through modulation of gene expression [54]. Meanwhile, QSI is disrupting bacterial communication by interfering with the production and sensing of autoinducers through small molecules [55]. Both seeds extract of *P. corylifolia* and bakuchiol displayed quorum sensing inhibitory activity as well as inhibition of biofilm formation of *Pseudomonas aeruginosa* PAO1, *Chromabacterium violaceum* CV12472, *Serratia marcescens*, and *Listeria monocytogenes* at a sub-lethal concentration [11]. This result highlighted the antibacterial potential of *P. corylifolia* extract and its phytoconstituent bakuchiol, targeting a reduction of biofilm formation and QS-associated virulence.

3.3 Anti-inflammatory Activity

In a study performed by Kim *et al*. (2016), seven major secondary metabolites from seeds of *P. corylifolia* included psoralen, isopsoralen, neobavaisoflavone, psoralidin, isobavachalcone, bavachinin, and bakuchiol were assessed for their neuroprotective and inhibition of neuroinflammation effects. Isopsoralen, isobavachalcone, and bakuchiol exhibited the most significant effect in suppressing nitric oxide (NO) production in lipopolysaccharide (LPS)-treated BV-2 cells in a dose-dependent manner. Meanwhile, neobavaisoflavone and bakuchiol showed better inhibition in H_2O_2-treated HT22 cells compared to other tested metabolites [25]. The neuroinflammation process has been identified to associate with many neurodegenerative diseases [56]. Therefore, targeting inflammation mediators such as NO and H_2O_2 involved in this process is promising for the therapy of neurodegenerative diseases. Excess of NO production leads to the generation of reactive nitrogen species and eventually neuronal cell death, while the presence of H_2O_2 induced neuronal cell death through oxidative stress [57], [58]. Altogether, among the tested compounds, bakuchiol was found as the most active metabolite for its neuroprotective and neuroinflammation inhibitory effects [25], which can be considered a potential candidate for neurodegenerative diseases.

Furthermore, three new isoflavone derivatives namely 7-O-methylcorylifol A, 7-O-isoprenylcorylifol A, and 7-O-isoprenylneobavaisoflavone, along with bakuchiol, 12,13-dihydro-12,13-epoxybakuchiol, psoralidin and other known compounds were reported from fruits of *P. corylifolia*. When tested for their anti-inflammatory potency against LPS-induced NO production in RAW264.7 cells, bakuchiol displayed the most potent inhibitory effect with an IC_{50} value of 21.57 µM [21], consistent with its activity reported before [25]. Meanwhile, psoralidin, 7-O-isoprenylcorylifol A and 12,13-dihydro-12,13-epoxybakuchiol showed lower inhibition of NO production with IC_{50} values of 27.46; 33.15 and 36.65 µM, respectively [21]. In addition, bakuchiol was found to have remarkable protective effect on sepsis-induced acute kidney inflammation through inhibition of NF-kB and p38 MAPK signaling in kidneys [41]. These results highlight the organ protective effects of *P. corylifolia* and its bioactive metabolites as a result of their anti-inflammatory action.

3.4 Hepatoprotective Effect

Psoralea corylifolia has been used in TCM to strengthen yang of kidneys and spleen, especially in pediatric diseases. Pharmacological investigation of *P. corylifolia* granules on nonalcoholic steatohepatitis in juvenile mice indicated that oral administration of this natural product was able to improve liver fibrosis at the dosage of 2.25 mg/g/d. Moreover, HPLC analysis indicated furanocoumarins, psolaren and isopsoralen as major active constituents of the tested *P. corylifolia* granules, most likely contributing to its hepatoprotective

activity. This substance acted through inhibition of the hepatic NF-kB signaling pathway and downregulated PI3K-Akt signaling pathway, leading to the reduction of hepatic inflammation [59].

Consistent with the previous study, ethanol extract of *P. corylifolia* seeds at a dosage of 200 mg/kg also revealed its potential effect in the prevention of nonalcoholic fatty liver disease (NAFLD) based on in vivo study on high fat diet-induced liver damage in mice. Administration of extract reduced lipid accumulation in the liver and downregulated the expression of proteins involved in hepatic inflammation. Flavonoids, neobavaisoflavone, bavachinin, corylin and corylifol A, were identified as major constituents of this active extract based on LC-MS analysis, while furanocoumarin, psoralidin was found in the lower amount [60].

3.5 Antidiabetic and Antiobesity

A meroterpene bakuchiol, together with five flavonoids identified as bavachin, bavachinin, 7,8-dihydro-8-(4-hydroxyphenyl)-2,2-dimethyl 2H,6H-benzo-[1,2-b:5,4-b′] dipyran-6-one, corylin, and kanzonol were isolated from ethyl acetate fraction of *P. corylifolia* fruits and were investigated for their antidiabetic potency. Among others, bavachin significantly enhanced proliferator-activated receptor γ (PPARγ) transcriptional activity and increased lipid accumulation in a dose-dependent manner. A further mechanistic study showed bavachin facilitated insulin-induced glucose uptake through activation of the insulin signaling pathway in differentiated adipocytes [61], indicating its therapeutic potential for type 2 diabetes mellitus.

Water-soluble extract of *P. corylifolia* seeds was found to have a protective effect against diabetic nephropathy in the assay involving streptozotocin-induced diabetic mice. Following oral administration of the extract, the expression of several genes associated with renal fibrosis and apoptosis was down-regulated, indicating its antifibrotic and antiapoptotic effects. The extract was also reported for its inhibition towards mesangial cell death, similar to that observed upon treatment with its main metabolites, psoralen, isopsoralen and bakuchiol [35]. Furthermore, Zhu *et al*. (2019) reported three new flavonoids identified as ((2Z)-2-[(4'-hydroxyphenyl) methylene]-6-hydroxy-7-prenyl-3(2H)-benzofurane), ((2S)-7-methoxy-6-(2-hydroxy-3-methyl but-3-en-1-yl)-2-(4-hydroxyphenyl) chroman-4-one and (2S)-4'-hydroxyl-7-hydroxymethylene-6-(2'',3''-epoxy-3''-methylbutyl) flavanone) with IC_{50} values of 35.2±1.3, 51.3±1.1, and 43.4±0.7 μM, respectively, along with a new coumestan, bavacoumestan E and eleven known metabolites from seeds of *P. corylifolia*. When evaluated for their antidiabetic potency, all of the newly isolated flavonoids exerted significant inhibition of diacylglycerol acyltransferase 1 (DGAT1) [38]. Two isoforms of DGAT (DGAT 1 and 2) are known as key enzymes involved in the triacylglycerol (TG) synthesis pathway. Targeting DGAT1 is considered to be prospective for controlling obesity and diabetes [62]. Meanwhile, the known coumestans, bavacoumestans B and C, showed significantly higher inhibition against protein tyrosine phosphatase 1B (PTP1B) with IC_{50} values of 24.1±0.7 and 10.2±0.9 μM, as well as stronger inhibition against α-glucosidase (IC_{50} values of 23.0 and 69.8 μM), in comparison to other isolated natural products [38].

In line with previous findings on antidiabetic potency of flavonoids from *P. corylifolia* [38], [61], a standardized flavonoid-rich fraction of *P.corylifolia* seeds was reported for its promising effect in obese mice induced by a high-fat supplemented diet. Administration of flavonoid-rich fraction led to a significant reduction of body weight, fat mass and improved insulin sensitivity. Its action is due to the promotion of several thermogenic gene expressions contributing to the prevention of obesity. This flavonoid fraction also improved glucose homeostasis through activation of insulin signaling and glucose transport in adipose tissue [63].

Moreover, two new meroterpenes, 7β, 13β-psoracorylifol B and 7β, 8α-psoracorylifol D were isolated from seeds of *P. corylifolia* in a recent study. These compounds demonstrated weak to moderate inhibition against DGAT1 [42], showing the potency of meroterpene analogues from *P. corylifolia* as DGAT inhibitors. Additionally, bavacoumestan D, a new coumestan reported from ethyl acetate extract of *P. corylifolia* seeds displayed moderate inhibition against DGAT1. Bavacoumestan D

also moderately inhibited α-glucosidase [30], following the activity reported before for its analogues bavacoumestans B and C [38].

3.6 Estrogenic Activity

Plant derived-natural products bearing structural similarity to endogenous estrogens and possessing estrogenic activity are collectively called phytoestrogens. Phytoestrogens are also known to contribute to various biological activities including antiproliferative, osteoporosis, improving menopause syndrome, and cardiovascular diseases. Isoflavones, coumestans, stilbenes and lignans are phenolic compounds repeatedly reported for their estrogenic properties [64]. Several flavonoids from the fruits of *P. corylifolia* are studied for their estrogenicity activity by Zhang *et al*. (2018). The tested flavonoids included isoflavones (corylin and neobavaisoflavone), flavanones (bavachin, isobavachin, and bavachinin), and chalcones (bavachalcone, isobavachalcone, and 4'-O-methylbavachalcone). In a fluorescence polarization assay, all of the tested flavonoids showed the binding ability to protein human estrogen receptor ligand-binding domain (hER-LBD) in a dose-dependent manner, except for corylin where no binding potency was found. Among the active flavonoids, neobavaisoflavone showed the highest binding capacity towards hER-LBD. A quantitative structure-activity relationship (QSAR) study indicated the presence of hydroxyl and prenyl groups are essential for the estrogenic activities of flavonoid compounds as evidenced by the absence of activity in corylin [23].

3.7 Osteoporosis Management

Osteoporosis is a metabolic bone disease due to decreased bone mass, deterioration of bone microstructural leading to bone fragility [65]. The potential therapeutic effect of *P. corylifolia* in osteoporosis management has been proven in previous studies. Neobavaisoflavone isolated from *P. corylifolia* was reported for its osteogenic activity. Its action on osteogenesis stimulation has occurred through activation of p38 followed by up-regulation of transcription factors Runx2 and Osx [66]. Furthermore, ethanolic extract of *P. corylifolia* seeds significantly regulated 18 potential biomarkers related to the pathogenesis of osteoporosis in glucocorticoid-induced osteoporosis rats. These biomarkers were found to be involved in tryptophan, nicotinamide and arginine metabolism pathways [67]. The effect of *P. corylifolia* extract in the regulation of these metabolic pathways and their corresponding biomarkers provided evidence for its potential therapeutic use for osteoporosis treatment.

Relevant to the previous finding on neobavaisoflavone, flavonoid fraction of *P. corylifolia* fruits was reported for its anti-osteoporosis in a recent study involving ovariectomized rats. HPLC analysis of this flavonoid fraction indicated neobavaisoflavone as the main flavonoid constituent of the fraction, whereas bavachin, corylin, isobavachalcone, bavachinin, and corlyfol A presented in much lower amounts. Of note, bone density and the trabecular microstructure are common parameters of bone quality useful for the diagnosis of osteoporosis. Bone homeostasis depends on bone formation by osteoblasts and bone resorption associated with osteoclasts [68]. Upon administration of flavonoid fraction of *P. corylifolia* fruits, increasing bone volume and decreasing trabecular spacing were observed. At the molecular level, expression of Runx2 was up-regulated and subsequently the number of osteoclasts decreased, whereas the ratio of OPG/RANKL in osteoblasts enhanced. Taken together, the flavonoid fraction of *P. corylifolia* fruits demonstrated its anti-osteoporosis activity through activation of osteogenesis [28].

In addition to neobavaisoflavone, corylin from *P. corylifolia* fruits was shown to have osteogenic activity. Corylin appeared to trigger the expression of important biomarkers in osteogenesis including Runx2, Osterix, Co11 and ALP. Detailed investigation on its mode of action revealed its osteogenic activity involved two pathways through estrogen and Wnt/β-catenin signaling, suggesting its therapeutic potential for osteoblasts-mediated osteoporosis [31].

3.8 Cytotoxic Activity

Several meroterpenes from *P. corylifolia* were known for their cytotoxic effects on various cancer cell lines. In a recent study performed by Xu *et al*. (2020), bakuchiol and its newly discovered cyclic derivatives from *P.*

corylifolia fruits, corypsoriols A–N, were investigated for their cytotoxicity against a panel of cancer cell lines (NCI-N87, HepG2, HCT-116, HeLa, and B16-F10 cells). Among the tested meroterpenoids, bakuchiol showed the highest inhibition against all tested cancer cell lines with IC_{50} values 6.24–19.53 μM, and no cytotoxic activity was observed for its new cyclic analogues [69]. This result indicates cyclization of side-chain diminished cytotoxic activity of meroterpenoid metabolites of *P. corylifolia*. Furthermore, another chemical investigation on *P. corylifolia* fruits performed by Xu *et al*. (2020) yielded 17 meroterpene phenols, of which the trivial name psocorylins A-Q were attributed for those new meroterpene analogues. In the cytotoxicity assay against a series of cancer cell lines (NCI-N87, HepG2, HCT-116, HeLa and B16-F10 cells), psocorylins B–E, F, M, and Q demonstrated remarkable cytotoxic activities with IC_{50} values less than 10 μM [33].

4 Conclusions

This paper included 63 bioactive natural products reported from seeds and fruits of *P. corylifolia*, belonging to flavonoids, furanocoumarins, meroterpenes, coumestans and steroids. Among them, bakuchicin, psoralen, isopsoralen, psoralidin, bakuchiol, neobavaisoflavone and corylin exhibited pronounce activity in numerous bioassays. These bioactive compounds are repeatedly reported for various biological activities such as improving skin disorder, antibacterial, anti-inflammatory, antidiabetic, antiobesity hepatoprotective, cytotoxic and estrogenic activities, promising for future applications in cosmetic and pharmaceutical fields. Detail investigation to uncover the mode of action of pharmacologically promising secondary metabolites from *P. corylifolia* is needed to provide comprehensive scientific evidence for future development.

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6 Author Contribution

Elizabeth S. P. Ratnasantasyacitta: conceptualization, writing original draft; Ni Putu Ariantari: conceptualization, writing, review, editing, supervision and funding acquisition. The authors have read and agreed the final version of the manuscript.

7 Conflicts of Interest

The authors declare no conflict of interest.

8 References

[1] M. N. Dludlu, A. M. Muasya, S. B. M. Chimphango, and C. H. Stirton, 2015. Taxonomy of the southern African *Psoralea aphylla* complex (Psoraleae, Leguminosae). *South African J. Bot.* 97. 77–100. doi: 10.1016/j.sajb.2014.11.009.

[2] P. Pandey, R. Mehta, and R. Upadhyay, 2013. Physiochemical and preliminary phytochemical screening of *Psoralea corylifolia*. *Arch. Appl. Sci. Res.* 5(2). 261–265.

[3] T. H. Won, I.-H. Song, K.-H. Kim, W.-Y. Yang, S. K. Lee, D.-C. Oh, W.-K. Oh, K.-B. Oh, and J. Shin, 2015. Bioactive metabolites from the fruits of *Psoralea corylifolia*. *J. Nat. Prod.* 78(4). 666–673. doi: 10.1021/np500834d.

[4] C.-C. Li, T.-L. Wang, Z. Q. Zhang, W.-Q. Yang, Y.-F. Wang, X. Chai, C.-H. Wang, and Z. Li, 2016. Phytochemical and pharmacological studies on the genus Psoralea: a mini review. *Evidence-based Complement. Altern. Med.*. 2016. doi: 10.1155/2016/8108643.

[5] J. Sharifi-Rad, S. Kamiloglu, B. Yeskaliyeva, A. Beyatli, M. A. Alfred, B. Salehi, D. Calina, A. O. Docea, M. Imran, N. V. A. Kumar, M. E. Romero-Roman, A. Maroyi, and M. Martorell, 2020. Pharmacological activities of psoralidin: a comprehensive review of the molecular mechanisms of action, *Front. Pharmacol.* 11. doi: 10.3389/fphar.2020.571459.

[6] S. Ma, Y. Huang, Y. Zhao, G. Du, L. Feng, C. Huang, Y. Li, and F. Guo, 2016. Prenylflavone derivatives from the seeds of *Psoralea corylifolia* exhibited PPAR-γ agonist activity. *Phytochem. Lett.* 16. 213–218. doi: 10.1016/j.phytol.2016.04.016.

[7] E. Seo, E. K. Lee, C. S. Lee, K. H. Chun, M. Y. Lee, and H. S. Jun, 2014. *Psoralea corylifolia* L. seed extract ameliorates streptozotocin-induced diabetes in mice by inhibition of oxidative stress. *Oxid. Med. Cell. Longev.* 2014. doi: 10.1155/2014/897296.

[8] M. J. Archarya, T. R. Singh, and B. J. Patgiri, 2015. Anti microbial activity of different dosage forms of Bakuchi (*Psoralea corylifolia* Linn.) taila, an

Ayurvedic formulation. *Int. J. Ayurvedic Med.* 6(3). 232–236. doi: 10.47552/ijam.v6i3.637.

[9] X. Ma and J. Meredith, 2021. *Herbal medicine in andrology: an evidence-based update*, A. Henkel, Ralf; Agarwal, Ed. Academic Press. Cambridge.

[10] Y. Han, H. Lee, H. Li, and J. H. Ryu, 2020. Corylifol a from *Psoralea corylifolia* L. enhances myogenesis and alleviates muscle atrophy. *Int. J. Mol. Sci.* 21. 5. 1–12. doi: 10.3390/ijms21051571.

[11] F. M. Husain, I. Ahmad, F. I. Khan, N. A. Al-Shabib, M. H. Baig, A. Hussain, M. T. Rehman, M. F. Alajmi, and K. A. Lobb, 2018. Seed extract of *Psoralea corylifoli*a and its constituent bakuchiol impairs AHL-based quorum sensing and biofilm formation in food- and human-related pathogens. *Front. Cell. Infect. Microbiol.* 8. 351. doi: 10.3389/fcimb.2018.00351.

[12] S. Shrestha, H. R. Jadav, P. Bedarkar, B. J. Patgiri, C. R. Harisha, S. Y. Chaudhari, and P. K. Prajapati, 2018. Pharmacognostical evaluation of *Psoralea corylifolia* Linn. seed. *J. Ayurveda Integr. Med.* 9(3). doi: 10.1016/j.jaim.2017.05.005.

[13] L. Tang, F. Guan, and D. He, 2012. Preliminary research on the interaction between a novel designed self-assembling peptide with half-sequence ionic complement and the natural product psoralen. *Adv. Mater. Res.* 550–553. 1580–1585. doi: 10.4028/www.scientific.net/AMR.550-553.1580.

[14] L. M. Madigan and H. W. Lim, *Psoralen-ultraviolet light a therapy*. Elsevier, 2016.

[15] A. Borate, A. Khambhapati, M. Udgire, D. Paul, and S. Mathur, 2014. Preliminary phytochemical studies and evaluation of antibacterial activity of *Psoralea corylifolia* seed extract. *Am. J. Phytomedicine Clin. Ther.* 2(1). 095–101.

[16] Q. Xu, Y. Pan, L.-T. Yi, Y.-C. Li, S.-F. Mo, F.-X Jiang, C.-F. Qiao, H.-X. Xu, X.-B. Lu, L.-D. Kong, and H.-F. Kung, 2008. Antidepressant-like effects of psoralen isolated from the seeds of *Psoralea corylifolia* in the mouse forced swimming test. *Biol. Pharm. Bull.* 31(6). 1109–1114. doi: 10.1248/bpb.31.1109.

[17] X. Yuan, Y. Bi, Z. Yan, W. Pu, Y. Li, and K. Zhou, 2016. Psoralen and isopsoralen ameliorate sex hormone deficiency-induced osteoporosis in female and male Mic. *Biomed Res. Int.* 2016. doi: 10.1155/2016/6869452.

[18] X. Li, C. Yu, Y. Hu, X. Xia, Y. Liao, J. Zhang, H. Chen, W. Lu, W. Zhou, and Z. Song, 2018. New application of psoralen and angelicin on periodontitis with anti-bacterial, anti-inflammatory, and osteogenesis effects, *Front. Cell. Infect. Microbiol.* 8. 1–13. doi: 10.3389/fcimb.2018.00178.

[19] Y. Wang, C. Hong, C. Zhou, D. Xu, and H. Bin Qu, 2011. Screening antitumor compounds psoralen and isopsoralen from *Psoralea corylifolia* L. seeds. *Evidence-based Complement. Altern. Med.* 2011. doi: 10.1093/ecam/nen087.

[20] K. Jafernik, E. Halina, S. Ercisli, and A. Szopa, 2021. Characteristics of bakuchiol- the compound with high biological activity and the main source of its acquisition- *Cullen corylifolium* (L.) Medik. *Nat. Prod. Res.* 35(24). 5828–5842. doi: 10.1080/14786419.2020.1837813.

[21] C. H. Chen, T. L. Hwang, L. C. Chen, T. H. Chang, C. S. Wei, and J. J. Chen, 2017. Isoflavones and anti-inflammatory constituents from the fruits of *Psoralea corylifolia*. *Phytochemistry*. 143.186–193. doi: 10.1016/j.phytochem.2017.08.004.

[22] Z. J. Chen, Y. F. Yang, Y. T. Zhang, and D. H. Yang, 2018. Dietary total prenylflavonoids from the fruits of *Psoralea corylifolia* L. prevents age-related cognitive deficits and down-regulates Alzheimer's markers in SAMP8 mice. *Molecules*. 23(1). doi: 10.3390/molecules23010196.

[23] T. Zhang, S. Zhong, Y. Meng, W. Deng, L. Hou, Y. Wang, X. Xing, T. Guan, J. Zhang, and T. Li, 2018. Quantitative structure-activity relationship for estrogenic flavonoids from *Psoralea corylifolia*, *J. Pharm. Biomed. Anal.*, 161, 129–135, doi: 10.1016/j.jpba.2018.08.040.

[24] A. K. Gebremeskel, T. D. Wijerathne, J. H. Kim, M. J. Kim, C.-S. Seo, H.-K. Shin, and K. P. Lee, 2017. *Psoralea corylifolia* extract induces vasodilation in rat arteries through both endothelium-dependent and -independent mechanisms involving inhibition of TRPC3 channel activity and elaboration of prostaglandin. *Pharm. Biol.* 55(1). 2136–2144. doi: 10.1080/13880209.2017.1383484.

[25] Y. J. Kim, H. Lim, J. Lee, and S. Jeong, 2016. Quantitative analysis of *Psoralea corylifolia* Linne and its neuroprotective and anti-neuroinflammatory effects in HT22 Hippocampal cells and BV-2 microglia. *Molecules*. 21. 1–11. doi: 10.3390/molecules21081076.

[26] Y. Li , X. Qin, P. Li, H. Zhang, T. Lin, Z. Miao, and S. Ma., 2019. Isobavachalcone isolated from *Psoralea corylifolia* inhibits cell proliferation and induces apoptosis via inhibiting the AKT/GSK-3β/β-catenin pathway in colorectal cancer cells. *Drug Des. Devel. Ther*. 13. 1449–1460. doi: 10.2147/DDDT.S192681.

[27] L. Zhou, J. Tang, X. Yang, H. Dong, X. Xiong, J. Huang, L. Zhang, H. Qin, and S. Yan, 2020. Five constituents in *Psoralea corylifolia* L. attenuate palmitic acid-induced hepatocyte injury via inhibiting the protein kinase C-α/nicotinamide-

adenine dinucleotide phosphate oxidase pathway, *Front. Pharmacol.* 10. 1–16. doi: 10.3389/fphar.2019.01589.

[28] B. Liu, X. Liu, Q. Ning, R. Zhong, Z. Xia, J. Li, J. Song, and Y. Wei, 2020. Evaluation of toxicity and anti-osteoporosis effect in rats treated with the flavonoids of Psoraleae fructus. *J. Funct. Foods*. 75. 104262. doi: 10.1016/j.jff.2020.104262.

[29] H. Z. Li, X. Meng, Y.-Y. Jiang, X. Lin, D.-X. Xiong, D. Wang, and H.-S. Lee, 2018. Four new flavonoids with DGAT inhibitory activity from *Psoralea corylifolia*. *Phytochem. Lett.* 28. 130–134. doi: 10.1016/j.phytol.2018.10.005.

[30] M. Y. Chai, 2019. A new bioactive coumestan from the seeds of *Psoralea corylifolia*. *J. Asian Nat. Prod. Res.*, 22(3). 295–301. doi: 10.1080/10286020.2018.1563073.

[31] A. X.-D. Yu, M. L. Xu, P. Yao, K. K.-L. Kwan, Y.-X. Liu, R. Duan, T. T.-X. Dong, R. K.-M. Ko, and K. W.-K. Tsim, 2020. Corylin, a flavonoid derived from Psoralea fructus, induces osteoblastic differentiation via estrogen and Wnt/β-catenin signaling pathways. *FASEB J*. 34(3). 4311–4328. doi: 10.1096/fj.201902319RRR.

[32] J. Du, C.-H Wang, J. Yang, X. He, X.-L. Han, C.-C. Li, X. Chai, Y.-F. Wang, Y. Zhu, and Z. Li, 2017. Chemical constituents from the fruits of *Psoralea corylifolia* and their protective effects on ionising radiation injury. *Nat. Prod. Res.* 33(5). 673–680. doi: 10.1080/14786419.2017.1405407.

[33] Q. X. Xu, Y. B. Zhang, X. Y. Liu, W. Xu, and X. W. Yang, 2020. Cytotoxic heterodimers of meroterpene phenol from the fruits of *Psoralea corylifolia*. *Phytochemistry*. 176(38). doi: 10.1016/j.phytochem.2020.112394.

[34] A. Alalaiwe, C.-F. Hung, Y.-L. Leu, K. Tahara, H.-H. Chen, K.-Y. Hu, and J.-Y. Fang, 2018. The active compounds derived from *Psoralea corylifolia* for photochemotherapy against psoriasis-like lesions: the relationship between structure and percutaneous absorption. *Eur. J. Pharm. Sci.* 124. 114–126. doi: 10.1016/j.ejps.2018.08.031.

[35] E. Seo, H. Kang, Y. S. Oh, and H. S. Jun, 2017. *Psoralea corylifolia* L. seed extract attenuates diabetic nephropathy by inhibiting renal fibrosis and apoptosis in streptozotocin-induced diabetic mice. *Nutrients*. 9(8). 1–12. doi: 10.3390/nu9080828.

[36] S. J. Kim, H. C. Oh, Y. C. Kim, G. S. Jeong, and S. Lee, 2016. Selective inhibition of bakuchicin isolated from *Psoralea corylifolia* on CYP1A in human liver microsomes. *Evidence-based Complement. Altern. Med.* 2016. 1–8. doi: 10.1155/2016/5198743.

[37] X. Li, Y. J. Lee, Y. C. Kim, G. S. Jeong, H. Z. Cui, H. Y. Kim, D. G. Kang, and H. S. Lee, 2011. Bakuchicin induces vascular relaxation via endothelium-dependent NO-cGMP signaling. *Phyther. Res.* 25(10). 1574–1578. doi: 10.1002/ptr.3478.

[38] G. Zhu, Y. Luo, X. Xu, H. Zhang, and M. Zhu, 2019. Anti-diabetic compounds from the seeds of *Psoralea corylifolia*. *Fitoterapia*. 139. 104373. doi: 10.1016/j.fitote.2019.104373.

[39] I. Hussain, N. Hussain, A. Manan, A. Rashid, B. Khan, and S. Bakhsh, 2016. Fabrication of anti-vitiligo ointment containing *Psoralea corylifolia*: in vitro and in vivo characterization. *Drug Des. Devel. Ther.* 10. 3805–3816. doi: 10.2147/DDDT.S114328.

[40] J. E. Kim, J. H. Kim, Y. Lee, H. Yang, Y.-S. Heo, A. M. Bode, K. W. Lee, and Z. Dong, 2016. Bakuchiol suppresses proliferation of skin cancer cells by directly targeting Hck, Blk, and p38 MAP kinase. *Oncotarget*. 7(12). 14616–14627. doi: 10.18632/oncotarget.7524.

[41] J. Wang, M. Luo, J. Shen, Z. Liu, Y. Chen, J. Luo, Z. Zeng, D. Deng, and J. Xiao, 2020. Bakuchiol from *Psoralea corylifolia* L. ameliorates acute kidney injury and improves survival in experimental polymicrobial sepsis. *Int. Immunopharmacol*. 89. doi: 10.1016/j.intimp.2020.107000.

[42] D. Wang, M.-X. Xiu, H.-Z. Li, D.-X. Xiong, H.-S. Lee, Y.-N. Sun, and L. Cui, 2020. Two new meroterpenes with activity against diacylglycerol acyltransferase from seeds of *Psoralea corylifolia*. *Phytochem. Lett.* 40. 171–175. doi: 10.1016/j.phytol.2020.10.006.

[43] L. Ren, L.-Z. Li, J. Huang, L.-Z. Huang, J.-H. Li, Y.-M. Li, and S.-Y. Tang, 2019. New compounds from the seeds of *Psoralea corylifolia* with their protein tyrosine phosphatase 1B inhibitory activity, *J. Asian Nat. Prod. Res.* 22(8). 732–737. doi: 10.1080/10286020.2019.1621852.

[44] X. Zhang, W. Zhao, Y. Wang, J. Lu, and X. Chen, 2016. The chemical constituents and bioactivities of *Psoralea corylifolia* Linn.: A review. *Am. J. Chin. Med.* 44(1). 35–60. doi: 10.1142/S0192415X16500038.

[45] I. Hussain and N. Mubarak, 2019. Skin pigmentation effects of *Psoralea corylifolia*: a case study of vitiligo. *J. Islam. Int. Med. Coll.* 14(1). 48–50.

[46] R. A. Spritz and G. H. L. Andersen, 2017. Genetics of vitiligo, *Dermatol. Clin.* 35(2). 245–255. doi: 10.1016/j.det.2016.11.013.

[47] S. Dhaliwal, I. Rybak, S. R. Ellis, M. Notay, M. Trivedi, W. Burney, A. R. Vaughn, M. Nguyen, P. Reiter, S. Bosanac, H. Yan, N. Foolad, and R. K. Sivamani, 2019. Prospective, randomized, double-blind assessment of topical bakuchiol and retinol for facial photoageing. *Br. J. Dermatol.* 180(2). 289–296. doi: 10.1111/bjd.16918.

[48] R. K. Chaudhuri and K. Bojanowski, 2014. Bakuchiol: a retinol-like functional compound revealed by gene expression profiling and clinically proven to have anti-aging effects. *Int. J. Cosmet. Sci.* 36. 221–230. doi: 10.1111/ics.12117.

[49] M. Shoji, Y. Arakaki, T. Esumi, S. Kohnomi, C. Yamamoto, Y. Suzuki, E. Takahashi, S. Konishi, H. Kido, and T. Kuzuhara, 2015. Bakuchiol is a phenolic isoprenoid with novel enantiomer-selective anti-influenza A virus activity involving Nrf2. *J. Biol. Chem*. 290(46). 28001–28017. doi: 10.1074/jbc.M115.669465.

[50] J. S. Lim, J. Y. Kim, S. Lee, J. K. Choi, E.-N. Kim, Y.-A. Choi, Y. H. Jang, G.-S. Jeong, and S.-H. Kim, 2020. Bakuchicin attenuates atopic skin inflammation. *Biomed. Pharmacother.*129. 0–7. doi: 10.1016/j.biopha.2020.110466.

[51] A. Dattola, L. Bennardo, M. Silvestri, and S. P. Nisticò, 2019. What's new in the treatment of atopic dermatitis? *Dermatol. Ther.* 32(2). 2–5. doi: 10.1111/dth.12787.

[52] M. Chong and L. Fonacier, 2015. Treatment of eczema: corticosteroids and beyond. *Clin. Rev. Allerg. Immunol*. 51(3). 249–262. doi: 10.1007/s12016-015-8486-7.

[53] H. N. Li, C. Y. Wang, C. L. Wang, C. H. Chou, Y. L. Leu, and B. Y. Chen, 2019. Antimicrobial effects and mechanisms of ethanol extracts of *Psoralea corylifolia* seeds against *Listeria monocytogenes* and methicillin-resistant *Staphylococcus aureus*. *Foodborne Pathog. Dis*. 16(8). 573–580. doi: 10.1089/fpd.2018.2595.

[54] S. T. Rutherford and B. L. Bassler, 2012. Bacterial quorum sensing: its role in rirulence and possibilities for its control. *Cold Spring Harb. Perspect. Med*. 2(11). 1–25. doi: 10.1101/cshperspect.a012427.

[55] B. Rémy, S. Mion, L. Plener, M. Elias, E. Chabrière, and D. Daudé, 2018. Interference in bacterial quorum sensing : A biopharmaceutical perspective. *Front. Pharmacol.* 9. doi: 10.3389/fphar.2018.00203.

[56] T. Kielian, 2015. Neuroinflammation: good, bad, or indifferent? *J. Neurochem*. 130(1). 1–3. doi: 10.1111/jnc.12755.Neuroinflammation.

[57] J. E. Yuste, E. Tarragon, C. M. Campuzano, and F. Ros-bernal, 2015. Implications of glial nitric oxide in neurodegenerative diseases. *Front. Cell. Neurosci.* 9. 1–13. doi: 10.3389/fncel.2015.00322.

[58] Z.-Y. Zhao, P. Luan, S.-X. Huang, S.-H. Xiao, J. Zhao, B. Zhang, B.-B. Gu, R.-B. Pi, and J. Liu, 2013. Edaravone protects HT22 peurons from H2O2-induced apoptosis by inhibiting the MAPK signaling pathway. *CNS Neurosci. Ther.* 19. 163–169. doi: 10.1111/cns.12044.

[59] L. Zhou, J. Tang, X. Xiong, H. Dong, J. Huang, S. Zhou, L. Zhang, H. Qin, and S. Yan, 2017. *Psoralea corylifolia* L. attenuates nonalcoholic steatohepatitis in juvenile mouse. *Front. Pharmacol.* 8. 1–13 doi: 10.3389/fphar.2017.00876.

[60] Y. M. Hong, S. I. Choi, E. Hong, and G. H. Kim, 2020. *Psoralea corylifolia* L. extract ameliorates nonalcoholic fatty liver disease in free-fatty-acid-incubated HEPG2 cells and in high-fat diet-fed mice. *J. Food Sci.* 85(7). 2216–2226. doi: 10.1111/1750-3841.15166.

[61] H. Lee, H. Li, M. Noh, and J. H. Ryu, 2016. Bavachin from *Psoralea corylifolia* improves insulin-dependent glucose uptake through insulin signaling and AMPK activation in 3T3-L1 adipocytes. *Int. J. Mol. Sci.* 17(4). doi: 10.3390/ijms17040527.

[62] S. He, Q. Hong, Z. Lai, D. X. Yang, P. C. Ting, J. T. Kuethe, T. A. Cernak, K. D. Dykstra, D. M. Sperbeck, Z. Wu, Y. Yu, G. X. Yang, T. Jian, J. Liu, D.Guiadeen, A. D. Krikorian, L. M. Sonatore, J. Wiltsie, J. Liu, J. N. Gorski, C. C. Chung, J. T. Gibson, J.-M. Lisnock, J. Xiao, M. Wolff, S. X. Tong, M. Madeira, B. V. Karanam, D.-M. Shen, J. M. Balkovec, S. Pinto, R. P. Nargund, and R. J. DeVita, 2014. Discovery of a potent and selective DGAT1 inhibitor with a Piperidinyl-oxy-cyclohexanecarboxylic acid moiety. *ACS Med. Chem. Lett.* 5(10). 1082–1087. doi: 10.1021/ml5003426.

[63] J. Liu, Y. Zhao, C. Huang, Y. Li, and F. Guo, 2019. Prenylated flavonoid-standardized extract from seeds of *Psoralea corylifolia* L. activated fat browning in high-fat diet–induced obese mice. *Phyther. Res.* 33(7). 1851–1864. doi: 10.1002/ptr.6374.

[64] D. Desmawati and D. Sulastri, 2019. Phytoestrogens and their health effect. *Maced. J. Med. Sci.* 7(3). 495–499. doi: 10.3889/oamjms.2019.086.

[65] T. Sözen, L. Özışık, and N. Ç. Başaran, 2017. An overview and management of osteoporosis. *Eur. J Rheumatol*. 4(1). 46–56. doi: 10.5152/eurjrheum.2016.048.

[66] M.-J. Don, L.-C. Lin, and W.-F. Chiou, 2012. Neobavaisoflavone stimulates osteogenesis via p38-mediated up-regulation of transcription factors and osteoid genes expression in MC3T3-E1 cells. *Phytomedicine.* 19(6). 551–561. doi: 10.1016/j.phymed.2012.01.006.

[67] F. J. Zhao, Z. B. Zhang, N. Ma, X. Teng, Z. C. Cai, and M. X. Liu, 2019. Untargeted metabolomics using liquid chromatography coupled with mass spectrometry for rapid discovery of metabolite biomarkers to reveal therapeutic effects of: Psoralea corylifolia seeds against

osteoporosis. *RSC Adv.* 9(61). 35429–35442. doi: 10.1039/c9ra07382e.

[68] S. A. Hienz, S. Paliwal, S. Ivanovski, B. Cells, and B. Homeostasis, 2015. Mechanisms of bone resorption in periodontitis. *J. Immunol. Res.* 2015. doi: http://dx.doi.org/10.1155/2015/615486.

[69] Q. Xu, W. Xu, and X. Yang, 2020. Meroterpenoids from the fruits of *Psoralea corylifolia*. *Tetrahedron*. 76. 31–32. doi: 10.1016/j.tet.2020.131343.