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A review of phytoconstituents and biological activities of genus *Phalaris*

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Abstract

Phalaris is a genus in the family Poaceae, which contains around 21 species. The members of this genus are used in traditional folk medicine in the treatment of hypertension, diabetes mellitus, and obesity. The review aims to collect the previous phytochemistry and biological activities of the extracts. The data of the literature collected revealed the presence of different chemical classes such as flavonoids, phenolic acids, anthocyanins, alkaloids, diterpenes, fatty acids, and sterols that contribute to antioxidant, anti-diabetic, anti-hypertensive, anti-Alzheimer, anti-obesity, anti-bacterial, anti-inflammatory, cytotoxic activities, etc. Further studies are needed to investigate other species of *Phalaris*, isolate chemical compounds and study their biological activities.

Introduction

Poaceae (formally Gramineae) is the most important flowering plants, comprising of approximately 10000 species in nearly 660 genera worldwide and commonly known as the grass family. The plants of this family are herbs, rarely shrubs or trees. Twelve subfamilies are recognized, Pooideae is the largest one containing mainly around 3968 species in 202 genera, including *Phalaris* [1].

Phytochemistry of the Poaceae family (Graminaea) has drawn more attention in recent years due to the discovery of several phenolic compounds as lignans, flavonoids and flavolignan [2, 3].

Phalaris is a genus in the tribe Poeae (Poaceae), around 21 species distributed in north temperate zone mainly Mediterranean region such as *P. angusta* Nees ex Trin., *P. appendiculata* Schult., *P. aquatica* L., *P. arundinacea* L., *P. brachystachys* Link, *P. caesia* Nees, *P. californica* Hook & Arn., *P. canariensis* L., *P. caroliniana* Walt., *P. coerulescens* Desf., *P. lemmonii* Vasey, *P. lindigii* Baldini, *P. maderensis* (Menezes) Menezes, *P. minor* Retz, and *P. paradoxa* L. Genus *Phalaris* gets its name from Greek phalaros meaning shining. Some species are reported to have different classes of bioactive secondary metabolites including; alkaloids, phenolic acids, flavonoids, anthocyanins, fatty acids, diterpenes and sterols [4, 5].

The *Phalaris* genus is recognized to be utilized in several traditional medicine applications as a hepatoprotective and useful tea remedy for hypertension, diabetes, and hypercholesterolernia [6-10].

The current review is included three main sections, the first section includes of various chemical constituents and their occurrence within the *Phalaris* species, the second comprises the toxicity of some species, the third section shows the numerous biological studies of the genus *Phalaris*.

Methodology

Data of this literature were collected from databases like "Google Scholar", "PubMed", "Science Direct", "Scopus" and "Scifinder". The main search words used to collect data were "*Phalaris*", "biological activity", "bioactive compounds" and "toxicity" and different synonyms of species. This review revealed that only 5 species of *Phalaris* have been reported in the literature.

Taxonomical classification of *Phalaris* genus

Kingdom: Plantae – Plants
Subkingdom: Tracheobionta – Vascular plants
Superdivision: Spermatophyta – Seed plants
Division: Magnoliophyta – Flowering plants
Class: Liliopsida – Monocotyledons
Subclass: Commelinidae
Order: Cyperales
Family: Poaceae – Grass family
Subfamily: Pooideae
Genus: *Phalaris* L. – Canary grass [11]

Phytochemistry

Genus *Phalaris* is rich in different classes of secondary metabolites, including phenolics (phenolic acids, anthocyanins and flavonoids), sterols, diterpenes, alkaloids, amino acids, and polysaccharides. A comprehensive list of the previously isolated compounds from *Phalaris* species is presented in Table 1 and Figures 1-4.

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Table 1. A list of isolated compounds from genus *Phalaris*.

No	Compound	Plant source	Ref.
Flavonoids			
1	5,7-Dihydroxy-3',4',5'-trimethoxy flavone	*P. canariensis*	[12]
2	5,7-Dihydroxy-4',5'-dimethoxy flavone (Tricin)	*P. canariensis*	[12]
3	Quercetin	*P. canariensis*	[12]
4	Rutin	*P. canariensis*	[12]
5	Quercetin-3-*O*-glucoside	*P. canariensis*	[12]
Phenolic acids			
6	Gallic acid	*P. canariensis*	[12]
7	*p*-Coumaric acid	*P. canariensis*	[12]
Anthocyanins			
8	Cyanidin 3-(3",6"-dimalonylglucoside)	*P. arundinacea*	[13]
9	Peonidin 3-(6"-malonylglucoside)	*P. arundinacea*	[13]
10	Peonidin 3-(dimalonylglucoside)	*P. arundinacea*	[13]
Alkaloids			
11	Gramine	*P. arundinacea, P. aquatica*	[14-17]
12	5-methoxy gramine	*P. aquatic*	[15]
13	7- Methoxy gramine	*P. aquatica*	[15]
14	5,7-Dimethoxy gramine	*P. aquatica*	[15]
15	Hordenine (p-hydroxyphenethyldimethylamine)	*P. arundinacea*	[16, 18]
16	5-Methoxy-N-methyl tryptamine	*P. arundinacea*	[18]
17	5-Hydroxy N,Ndimethyl tryptamine (Bufotenine)	*P. tuberosa*	[19]
18	N,N-Dimethyl tryptamine	*P. tuberosa*	[19]
19	5-Methoxy- N, N-dimethyl tryptamine	*P. arundinaceae* *P. tuberosa*	[19]
20	(-)-Coerulescine	*P. coerulescens*	[20]
21	R-(-)-Horsfiline	*P. coerulescens*	[20]
22	Phalarine	*P. coerulescens*	[21]
23	2,9-Dimethyl-6-methoxy-1,2,3,4-tetrahydro-β-carboline	*P. arundinacea*	[16]
Diterpenes			
24	Abieta-8,11,13-triene-3β-acetyl-19-ol (Canarien A)	*P. canariensis*	[22]
25	Canarien B	*P. canariensis.*	[22]
26	Canarien C	*P. canariensis.*	[22]
27	14β,19-Diacetylpimara-15-ene	*P. canariensis.*	[23]
28	3β,19-Diacetylpimara-15-ene	*P. canariensis.*	[23]
29	1β,19-Diacetylpimara-15-ene	*P. canariensis.*	[23]
30	8β-Hydroxy-3β,19-diacetylpimara-15-ene	*P. canariensis.*	[23]
31	8β-Hydroxy-1α,19-diacetylpimara-15-ene	*P. canariensis.*	[23]
32	19-Hydroxy-3β,7β-diacetylpimara-15-ene	*P. canariensis.*	[23]
33	19-Hydroxy-3β,11α-diacetylpimara-15-ene	*P. canariensis.*	[23]
34	Abietatrien-3β-acetyl-6,19-olide	*P. canariensis.*	[23]
35	Abietatrien-3β-acetyl-2βol-6,19-olide	*P. canariensis.*	[23]
Carbohydrates			
36	Inulin	*P. arundinacea*	[24]
Fatty alcohol			
37	*n*-Octacosanol	*P. arundinacea*	[16]
Sterols			
38	*β*- Sitosterol	*P. canariensis*	[25]

1. Flavonoids and phenolic acids

This class of compounds has potent antioxidant properties [26]. 5,7-Dihydroxy-3',4',5'-trimethoxy flavone, 5,7-dihydroxy-4',5'-dimethoxy flavone (Tricin), quercetin, rutin and quercetin-3-*O*-glucoside (**1-5**) were isolated from chloroform and ethyl acetate fractions of *P. canariensis* seeds. Additionally, two phenolic acids; gallic acid and *p*-coumaric acid (**6, 7**) were reported for the first time from *P. canariensis* [12].

2. Anthocyanins

Three anthocyanins (**8-10**) were obtained from flowers of reed canary grass, *P. arundinacea* [13].

3. Alkaloids

Gramine (**11**) is a common indole alkaloid in Poaceae family and was isolated from *P. arundinacea* and root of *P. aquatic* and other gramine derivatives (**12-14**) were isolated from *P. aquatic* In addition of two oxindoles alkaloids and one furanobisindole type (**20-22**) were found in *P. coerulescens*, together with tryptamine derivatives (**16-19**) from *P. arundinacea* and *P. tuberosa*. Finally two other classes of alkaloids, phenethyl amine and tetrahydro-β-carboline, (**15, 23**) were found in *P. arundinacea* [14-21].

4. Diterpenes

Abietane diterpenes were isolated from hexane fraction of *P. canariensis* seeds including canarien A (**24**), abietatrien-3b-acetyl-6,19-olide (**34**) and abietatrien-3β-acetyl-2bol-6,19-olide (**35**) [22, 23] . Furthermore, diterpenes of pimaranes type were reported from hexane fraction of *P. canariensis* seeds such as canarien B (**25**), canarien C (**26**), 14β,19-diacetylpimara-15-ene (**27**), 3β,19-diacetylpimara-15-ene (**28**), 1β,19-diacetylpimara-15-ene (**29**), 8β-hydroxy-3β,19-diacetylpimara-15-ene (**30**), 8β-hydroxy-1α,19-diacetylpimara-15-ene (**31**), 19-hydroxy-3β,7β-diacetylpimara-15-ene (**32**), and 19-hydroxy-3β,11α-diacetylpimara-15-ene (**33**) [22, 23].

5. Others

One carbohydrate; inulin (**36**) was isolated from root of *P. arundinacea* [24], additionally a fatty alcohol; *n*-octacosanol (**37**) was obtained from whole plant of *P. arundinacea* [16]. *β*-Sitosterol (**38**) was found in *P. canariensis* [25].

Phalaris toxicity

Several studies have been reported regarding *Phalaris* toxicity on herbivores finding four types of symptoms of *Phalaris* toxicities, including acute and chronic staggers, which involve the *Phalaris* central nervous locomotor disorder, characterized by ataxia, muscle tremors, hyper-excitability, etc [27-29]. In addition to cardiac sudden death and poliencephalomalicia sudden death involves ammonia toxicity [27, 30].
The alkaloids that are found in high concentrations in some *Phalaris* species, including *P. aquatica, P. angusta, P. arundinacea, P. minor,* and *P. caroliniana,* are directly linked to the toxicity of the species. These alkaloids are primarily indole-derived tryptamine alkaloids, particularly N,N-dimethyltryptamine (DMT) and 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT), which have structures similar to serotonin and can cause dysfunction in both cardiac system and central nervous system.[27-33].

Biological activities of genus "*Phalaris*"

Phalaris species exhibited various biological activities including; anti-inflammatory, antihypertension, antioxidant, antimicrobial, cytotoxicity and antidiabetic activities….etc (Figure 5).

1. Antioxidant activity

The ethanol and acetone extracts of *Phalaris minor* were investigated for their antioxidant properties using the DPPH and ABTS radical scavenging capacity assays and the ROS superoxide radical assay. The ethanol extract revealed ABTS radical scavenging potential with IC_{50} value of 4.17 ± 0.37 μg/mL compared with ascorbic acid (2.80 ± 0.29 μg/mL) as a positive control [34].
The antioxidant activity of *Phalaris minor* extracts using various solvents such as methanol, acetone, chloroform, water, methanol-acetone, methanol-chloroform as well as methanol-water was evaluated. Methanol-chloroform exhibited DPPH scavenging, reducing power and hydrogen peroxide scavenging activities ($IC_{50} = 117.414$, 246.59 and 179.74μg/mL, respectively). The IC_{50} values were compared to the IC_{50} of ascorbic acid as reference (55.00, 6.89 and 148.48 μg/mL, respectively) [35].
Seed oils from the hexane extract of *P. canariensis,* prepared by maceration and ultrasonication exhibited a weak antioxidant activity compared with Vitamin E and BHT as positive standards using a DPPH radical scavenging capacity assay [36].
Antioxidant activity of extracts from the seed of P. canariensis, using three different solvents: hexane, ethyl acetate, and methanol was investigated using DPPH radical scavenging. The methanol extract showed the highest antioxidant activity (IC_{50} of 0.12 mg/mL), followed by the ethyl acetate extract (IC_{50} = 0.15 mg/mL), and finally the hexane extract (IC_{50} = 0.22 mg/mL) in comparison with Vit. E and BHT (IC_{50} values = 0.026 and 0.017 mg/mL, respectively) as standard antioxidants [37].
Ether extract from canary seeds has been shown to have the highest antioxidant activity and these compounds are known as esters of caffeic acid with sterols and triterpenes [38].
Canary seed peptides (CSP) had shown antioxidant activity after using DPPH and ABTS radical scavenging assays and found that low molecular weight, aromatic amino acids and other specific amino acids play a role in this antioxidant activity [39].
Antioxidant Activity of Canary Seed Peptides were investigated using ABTS and DPPH assays and found that milk samples (obtained from soaked seeds in distilled water for 12hr and 24hr) showed more antioxidant effect than the flour (obtained after ground of the seeds) [40]
The non-inulinic compounds from root extracts of *P. arundinacea* were examined by DPPH scavenging assay showing antioxidant activity through increasing protection against lipid peroxidation [24].

2. Antimicrobial activity

Ethanol extracts and acetone extracts of *P. minor* showed antibacterial activity through the disk diffusion method against *Staphylococcus aureus, Bacillus spizizenii, and Salmonella typhi,* but showed no activity against *Escherichia coli or Listeria monocytogenes* and antifungal activity against *Wickerhamomyces anomalus and Saccharomyces cerevisiae,* but showed no activity
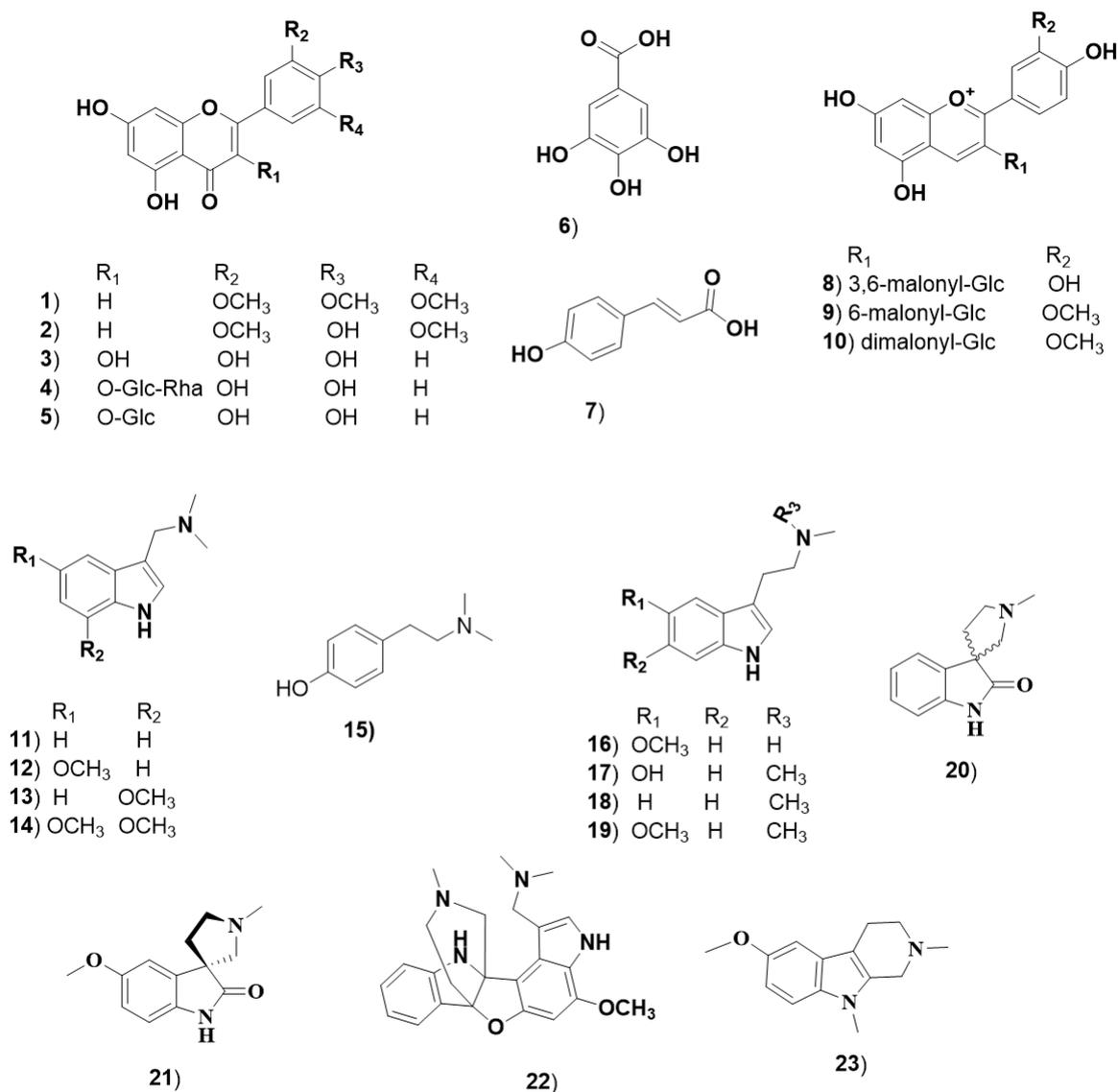
Figure 1. Structures of isolated compounds from *Phalaris* species (**1-23**).

against any type of these microorganisms of fungi as *Fusarium oxysporum, Mucor* species, *Aspergillus flavus, and Aspergillus niger* [34].

The antibacterial activity of *P. canariensis* (Methanol, ethyl acetate and hexane extracts) was evaluated using the disk diffusion method against bacteria strains from Gram-positive and Gram-negative and results compared with ampicillin (10 μg/disc) as a positive control. The methanol and ethyl acetate extracts of *P. canariensis* showed high antibacterial activity against *Micrococcus luteus.* The hexane and ethyl acetate extracts showed high antibacterial activity against *Bacillus subtilis.* The methanol extract showed antibacterial activity against *Listeria monocytogenes.* The hexane extract showed antibacterial activity against *Salmonella sp.* While *Escherichia coli 25922* and *Enterococcus faecalis* showed resistance to all extracts [37].

The antibacterial activity of *P. canariensis* seed oils was evaluated against different bacterial strains with the disc-diffusion assay method and showed antibacterial activity only against *Bacillus subtilitis* and *Salmonella sp* [36].

3. Reno-protective activity

Ethanolic extract from *P. canariensis* seeds showed protective activity to the kidney from severe damage (nephrotoxicity) caused by methotrexate (MTX), used in treatment of cancer, through an increase in the anti-apoptotic protein BCL2 at doses of 200 and 400 mg/kg/d [12].

4. Antihyperglycemic activity

Canary seed peptides obtained from the hexane fraction of *P. canariensis* seed showed inhibition of dipeptidyl peptidase IV (DPP-IV), these peptides considered as a group of antihyperglycemic agents used to manage type 2 diabetes mellitus, with a percent of 43.4% when using a high concentration of 1.4 mg/mL [6].
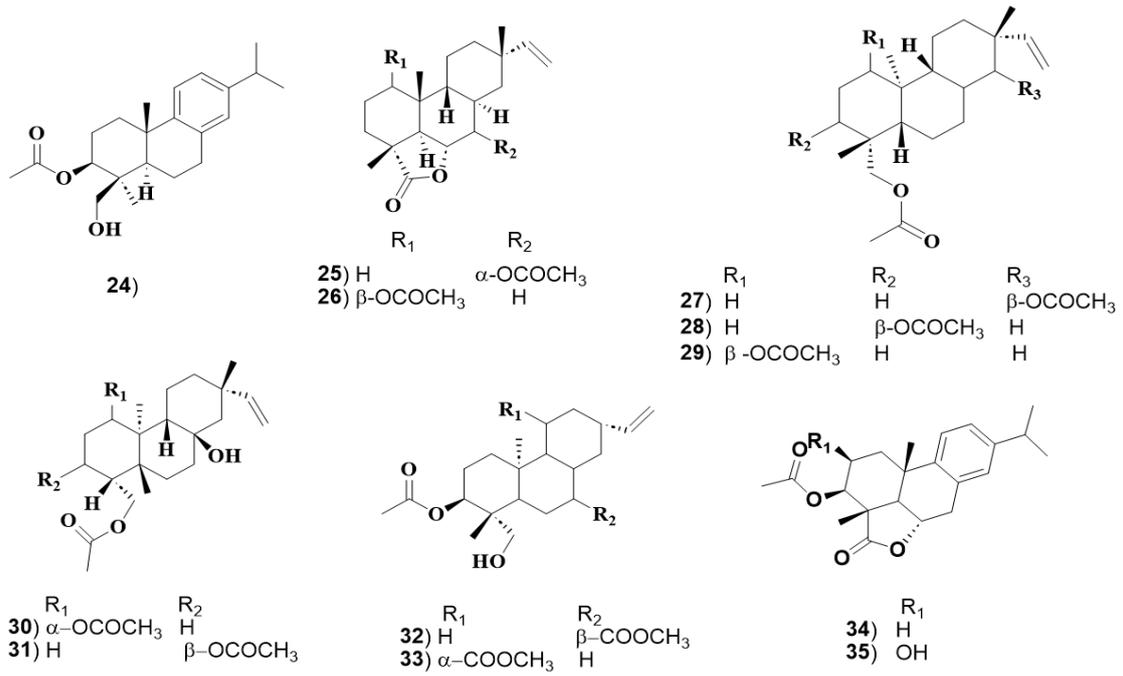
24)

	R₁	R₂
25)	H	α-OCOCH₃
26)	β-OCOCH₃	H

	R₁	R₂	R₃
27)	H	H	β-OCOCH₃
28)	H	β-OCOCH₃	H
29)	β-OCOCH₃	H	H

	R₁	R₂
30)	α–OCOCH₃	H
31)	H	β–OCOCH₃

	R₁	R₂
32)	H	β–COOCH₃
33)	α–COOCH₃	H

	R₁
34)	H
35)	OH

Figure 2. Structures of isolated diterpenes from *Phalaris* species (**24-35**).

36)

37)

38)
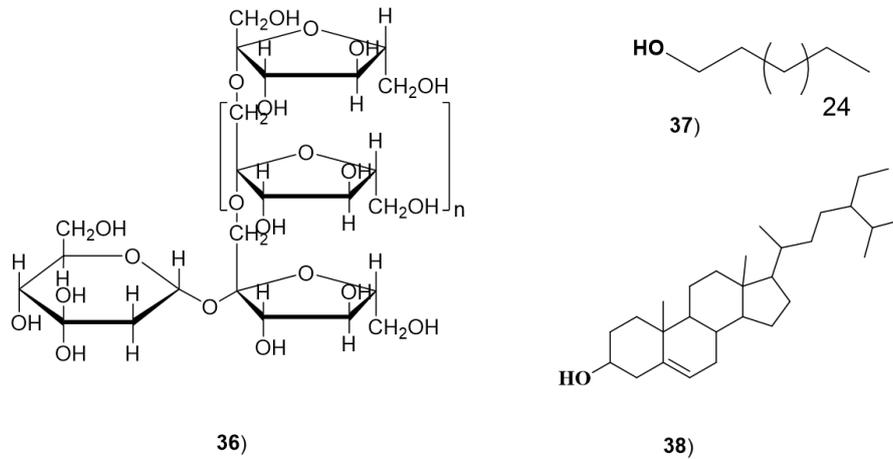
Figure 3. Structures of isolated compounds from *Phalaris* species (**36-38**).

Flavonoids — 13%
Phenolic acids — 5%
Anthocyanins — 8%
Alkaloids — 34%
Diterpenes — 31%
Carbohydrates — 3%
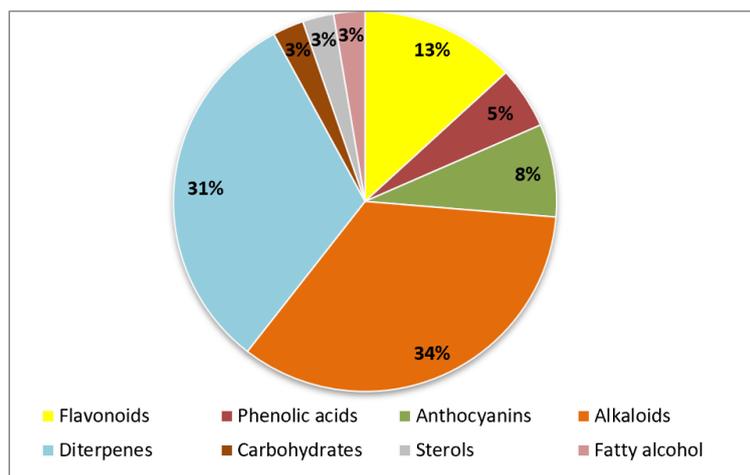Sterols — 3%
Fatty alcohol — 3%

Figure 4. Different classes of compounds in plants of the genus *Phalaris*

In the treatment of type 2 diabetes mellitus (T2DM), protein tyrosine phosphatase 1B (PTP1B) has garnered significant attention as a crucial negative modulator of insulin signaling [41]. Diterpenes that were isolated from the hexane fraction of canary seeds (*P. canariensis),* especially those with an acetyl group at C-19, showed the highest inhibitory activity against protein tyrosine phosphatase 1B (PTP1B), with IC_{50} values of 6.5±1.43, 6.9±2.07 and 7.3± 2.21 μM for compounds **27, 29,** and **28,** respectively, when compared with the IC_{50} for RK-682 (3-hexadecanoyl-5-hydroxymethyl-tetronic acid), which has a 4.8± 0.95 μM value [41].

The antidiabetic activity of diterpenes (**27-33**) isolated from the hexane fraction of *P. canariensis* seeds was determined by streptozotocin-nicotinamide induced diabetic mice. The results were then compared with standard glibenclamide (5 mg/kg) and found that the maximum effect on blood glucose reduction was achieved with 20 mg/kg at 6 h. This suggests the use of *P. canariensis* extract in folk medicine as a coadjutant in the treatment of diabetes mellitus [41].

Canary seed peptides of (*P. canariensis)* firstly reported to have capacity against α-glucosidase enzyme that contributes to preventing the rise in glucose after a meal, and any complication related to diabetes with IC_{50} =1.15 and 0.82 mg/mL for < 3KDa and 3-10 kDa [39].

5. Antihypertensive activity

Canary seed peptides have 73.5% inhibition against angiotensin converting enzyme (ACE) with an IC_{50} of 332 μg/mL, comparable to the standard captopril (used as a positive control) with an IC_{50} of 4.074 μg/mL [6].

Also, these peptides were able to induce the production of nitric oxide (NO) (12.24 μM), a potent vasodilator, at 1 μg/mL, at levels near what captopril (CPT) and bradykinin (BK) can produce [6].

Other studies on canary seed peptides have an IC_{50} of 217.4 μg/mL [40]. Small molecular weight fractions (< 3 kDa and 3–10 kDa) of canary seed peptides showed high inhibitory activity with IC_{50} values of 26.75 and 31.73 μg/mL [39].

6. Anti-obesity

Through the inhibition of enzymes linked to obesity, hexane and methanol extract demonstrated anti-obesity activity. Peptide responsible for this activity was discovered through additional research. Another study has been found that hexane fraction of *P. canariensis* at dose of 400 mg/kg showed hepatoprotective effect through reduced of hepatic enzymes (ALP: alkaline phosphatase; SGOT: serum glutamate oxaloacetate transaminase; SGPT: serum glutamate) and this contributed in the prevention of hepatic fatty deposition in hepatocytes [10, 39, 42].

7. Anti acetylcholinesterase activity

Seed oils prepared from *P. canariensis* by maceration and ultrasonication extraction methods showed ability to inhibit 60% and 55.4% of AChE (acetylcholinesterase), a new strategy for treatment of Alzheimer's disease, compared with Tacrine as a standard had 80.5% inhibition of AChE. This study suggested to that AChE inhibition may be in relation with sterols, phenolic, fatty acids from seeds oil [36].

Different extracts of *P. canariensis* including methanol, ethyl acetate and hexane were investigated for their AChE inhibition activity and the results compared to Tacrine as a standard at concentration of 0.1 mg/mL. The study showed that methanol extract had a strong percentage of inhibition (65.0%) at the concentration of 1 mg/mL against acetylcholinesterase (AChE) while ethyl acetate and hexane had moderate percentages of inhibition (25.4 and 45.8 % respectively) compared to Tacrine with inhibition percentage of 80.5%. This Activity of *Phalaris* extracts related to their content of polyphenols and flavonoids [37].

In these earlier studies, *P. canariensis* extracts were used for the first time to inhibit acetylcholinesterase in vitro and were found to have a potent effect in treating Alzheimer's disease [36, 37].
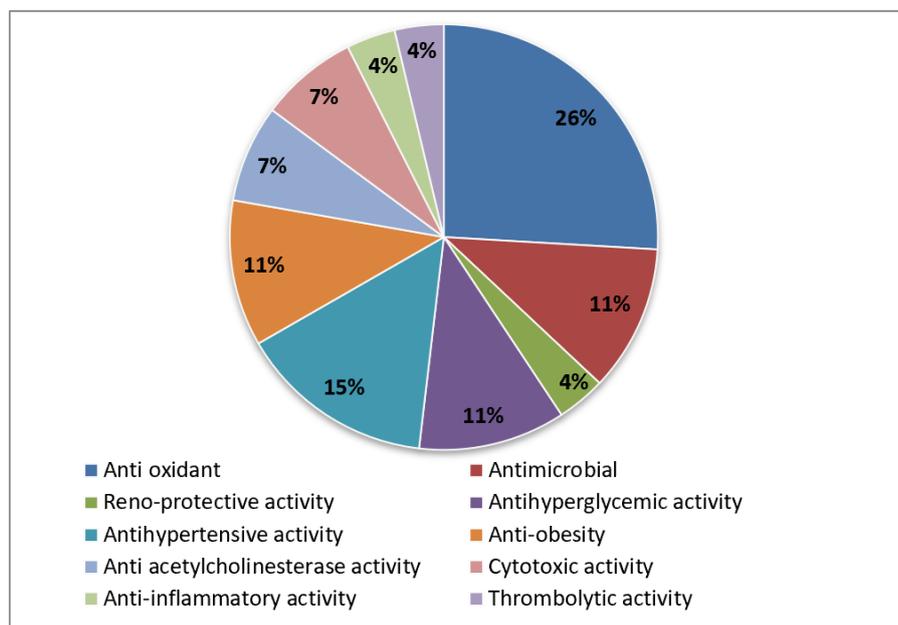

Figure 5. Different biological activities of plants of the genus *Phalaris*

8. Thrombolytic activity

The aqueous extract of *P. canariensis* seeds was investigated for thrombolytic activity. The maximum percentage of clot lysis, 82.04%, was observed with the aqueous extract. compared with Streptokinase that showed 66.77 % of clot lysis using method described by Daginawala [43].

9. Cytotoxic activity

Different extracts from the canary seed of *P. canariensis* can be used as cytotoxic agents, especially chloroform extract, which showed the highest lethality with a LC_{50} value of 94.58 μg/ml compared with a standard vincristine sulfate that showed a LC_{50} value of 0.45 μg/ml using the brine shrimp lethality test [43].

Using brine shrimp lethality, it was found that ethanol and acetone extracts of *P. minor* have LC_{50} values of 8.93 and 13.67 μg/mL, respectively [34, 44].

Ethanol extracts of *P. minor* (2, 4, and 6 μg/mL) have DNA-protecting ability from damage by radicals that are formed by adding fenton reagent [34].

10. Anti-inflammatory activity

The anti-inflammatory properties of *P. canariensis* chloroform extracts were investigated in four different models: carrageenan-induced oedema, histamine-induced inflammation, cotton pellet-induced granuloma, and croton oil-induced oedema in a dose-dependent manner. The results were compared with indomethacin as a reference, and all the models demonstrated significant anti-inflammatory activity.

Also ALC showed significantly decreased chemical mediators of inflammation and pro inflammatory cytokines such as TNFα, IL-1β, PGE2 and LTB4 and nitric oxide (NO). ALC had ability to suppress activity of myeloperoxidase (MPO) enzyme related to inflammation reaction [45].

Conclusion

The literature survey of different *Phalaris* species revealed the presence 38 compounds of different classes of phytoconstituents such as flavonoids (5), phenolic acids (2), anthocyanins (3), alkaloids (13), and diterpenes (12), which are the most abundant among the various species of *Phalaris*. Furthermore, three compounds belong to different classes of secondary metabolites sterols, fatty alcohol and polysaccharides. This review demonstrated the wide range of biological activities of *Phalaris* plants, including antioxidant, cytotoxic, antidiabetic, anti inflammatory, antimicrobial, and antihypertensive activities. Based on the current assessment, *Phalaris* plants require additional research to examine those that have not been studied phytochemically or biologically in order to expand our knowledge of these plants' phytopharmacology. Future research studies should also measure the various biological effects of Phalaris plants and their bioactive phytocompounds.

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