Phytochemistry, pharmacology and medicinal uses of plants of the genus : an updat...

Health & Medicine

Introduction

Salicaceae (the Willow and Poplar family) traditionally includes the genera *Populus* (poplar) and *Salix* (willow), which are common in Northern temperate regions, and are amentiferous (bearing catkins) (Isebrands and Richardson, 2014). Presently, the Salicaceae have been enlarged to contain most tropical members of Flacourtiaceae, which do not produce catkin (Thadeo et al., 2014). Thus, the family Salicaceae now comprises about 56 genera and 1, 220 species (Christenhusz and Byng, 2016).

The members of Salicaceae are fast growing trees or shrubs (Isebrands and Richardson, 2014). They are used for many economic purposes as production of timber, paper, fences, shelter, snowshoes, arrow shafts, fish traps, whistles, nets, rope, as a biomass fuel (a source of renewable energy), for ornamental, architectural and horticulture uses. Also, they are used for environmental enhancement through soil erosion control (Kuzovkina and Vietto, 2014). Willow twigs are elastic and were used to interweave baskets, for caning, and to manufacture woven fences and other lattices (Isebrands and Richardson, 2014).

The genus *Salix* (the willow) includes 330–500 species and more than 200 hybrids (Isebrands and Richardson, 2014), which are most widely distributed in the Northern hemisphere with a limited number of species occur in the Southern hemisphere (Zhen-Fu, 1987). *Salix* species are widely distributed in Africa, North America, Europe, and Asia (Argus, 2007). *Salix* species are fast growing trees, shrubs or prostrate plants; they can withstand a wide range of different weathers more than *Populus* species, as

they grow in temperate, subtropic and tropic regions (Isebrands and Richardson, 2014).

Taxonomy

General morphological characters of genus *Salix* were reported (Argus, 2006 ; Lauron-Moreau, et al., 2015). Willows are 6–10 m high trees or shrubs with spirally arranged, sometimes silvery, oblong leaves. The latter is commonly hairy on the underside and often turn black when drying. Leaves are simple, petiolate showing different shapes of lamina (oblong, linear, ovate, obovate or round), stipulate with linear to rounded stipules and with entire, serrate or dentate margin. Their arrangement is mostly alternate or rarely opposite (Lauron-Moreau, et al., 2015). The flowers are catkins, dioecious, with nectaries (glands) instead of perianth and they have bracts, which are pale or black, pubescent or glabrate, constant in male flowers and deciduous in female ones. The flowers blossom in spring, generally prior the leaves (Mabberley 2008). The male catkins have mostly two stamens, more prominent yellow, with few species having 3–12 stamens while the female catkins are greenish, have single pistil with single ovary, style, two-lobed stigma and 2 to 42 ovules per each ovary (Mabberley 2008). The nectar of flowering Willow is the first food source for bees in spring. The seeds are small, with limited longevity, fine hairy coat enabling their spread by wind and they germinate after few days of exposure to moistured surfaces (Mabberley 2008). Recently, the taxonomy of neotropical Salicaceae (formerly Flacourtiaceae) is difficult, as they show very different morphology and exhibit numerous characteristics in common with several other families. The neotropical Salicaceae and Salicaceae displayed similar characters such

as the presence of salicoid leaf teeth, collateral and arch-shaped vascular system at the midrib, abundance of crystals, brachyparacytic stomata, secondary growth of the petiole and sclerenchyma accompanying the bundles (Thadeo et al., 2014).

Phytochemistry

Different phytoconstituents or secondary metabolites of the genus *Salix* as flavonoids, glycosides (phenolic and non-phenolic glycosides), procyanidins, organic acids and their derivatives, simple phenolics, sterols and terpenes, lignans, volatiles and fatty acids were reported (Supplementary Tables S1–S7 , included in Supplementary materials). *Salix* leaves mainly contain flavonoids, phenolic acids, their derivatives, and phenolic glycosides, while stem bark mainly contains procyanidins.

Flavonoids

Salix contains a wide variety of flavonoids, which are distinctive for each species, as flavones, flavonols, flavanones, dihydroflavonols, isoflavones, chalcones, dihydrochalcones, flavan-3-ols and anthocyanins (Nasudari et al., 1972; Pobł ocka-Olech and Krauze-Shao et al., 1989; Du et al., 2004; Zeid, 2006; Jü rgenliemk et al., 2007; Baranowska, 2008; Freischmidt et al., 2010; Li et al., 2013). Data are summarized in Supplementary Table S1 and the structures are presented in Figure 1 .

FIGURE 1

Structures of reported flavonoids from the genus *Salix.*

The highest numbers of different classes of flavonoids (A-E) were detected in leaves and rarely in roots. The flavones as apigenin and its glycosides (1, 2, 4, 5) are major constituents of *S. acutifolia* Willd. leaves (Shelyuto and Bondarenko, 1985), *S. matsudana* Koidz. leaves (Han et al., 2003a) and *S. babylonica* L. leaves and roots (Khatoon et al., 1988 ; Singh et al., 2017). Whereas, chrysoeriol (6), its 7- *O* -D-glucoside 7) and 7- *O* -glucuronide 8) are major constituents of *S. babylonica* L. (Liu et al., 2008), *S. matsudana* Koidz. leaves (Han et al., 2003b) and *S. subserrata* Willd. leaves (Tawfeek et al., 2019), respectively. Compounds (12, 14) were reported in *S. denticulate* leav *es* (Rawat et al., 2009 ; Semwal et al., 2011). *S. gilgiana* Seemen. leaves were characterized by the accumulation of acylated luteolin glucosides (19–23) (Mizuno et al., 1987). Compounds (25, 35) are chemical markers for *S. matsudana* Koidz. leaves (Li et al., 2008). Kaempferol 32) and its 7, 4`-dimethyl derivative 33) were found to be most prominent constituents in *S. bordensis* Turcz. (Zhao et al., 2014). Also, kaempferol-7- *O* -glucoside 34) is a major compound in *S. babylonica* L. leaves and roots (Khatoon et al., 1988 ; Singh et al., 2017).

Angeloxyflavone 13) and isoflavones (63, 64) are chemical markers for *S. cheilophila* C. K. Schneid. twigs (Shen et al., 2008). *S. integra × S. suchowensis* young stem was characterized by the accumulation of sulfated flavanones and dihydroflavonol as compounds (49, 52, 58, 60). Compound 11) was reported in the erial parts of *S. denticulate* Andersson.

The highest number of chalcones, catechins, procyanidins and anthocyanins were detected in the bark of willows . The bark of *S. daphnoides* Vill. *, S.*

elbursensis Boiss. *, S. acutifolia* Willd. and *S. rubra* Huds. were characterized by the accumulation of chalcones (65–67) (Kompantsev, 1969 ; Kompantsev and Shinkarenko, 1975 ; Vinokurov, 1979 ; Zapesochnaya et al., 2002 ; Krauze-Baranowska et al., 2013). Catechin 69) and its derivatives (70, 71), epicatechin (72), procyanidin B1 77) and its derivative (78), procyanidin B3 (80) and its derivative (81), procyanidins B6 (84), B7 85) and trimeric procyanidins (87–89) were found to be major constituents of *S. sieboldiana* Blume bark (Hsu et al., 1985). Also, procyanidins (77, 79, 80, 82, 83, 85, 86, 89, 90, 92) are major constituents of *S. daphnoides* Vill. bark (Wiesneth, 2019). Anthocyanins (93–95) were detected in the bark of *S. purpurea* L., *S. daphnoides* Vill. *, S. alba* L. *, S. phylicifolia* L. *, S. nigricans* Sm. *, S. calodendron* Wimm. *and S. viminalis* L. *, S. triandra* L. and *S. amygdalina* L. (Bridle et al., 1970 ; Bridle et al., 1973).

Phenolic Glycosides

Glycosides are major secondary metabolites in Salicaceae (Binns et al., 1968; Kompantsev and Shinkarenko, 1973; Kompantsev et al., 1974; Nichols-Orians et al., 1992; Fernandes et al., 2009). Phenolic glycosides represent up to 30% of dry plant mass. They are classified into two main classes: Salicin derived glycosides (salicinoids) and other phenolic glycosides as glycosylated phenylpropanoids, phenylethanoids and benzenoids and glycosylated salicylic acid derivatives. Salicinoids, which are considered as taxonomic markers for genus *Salix* , are derivatives of salicin, produced by esterification of one or more hydroxyl groups of salicyl alcohol or glucose moieties, mainly 2` and/or 6′ of glucose, with organic acids as acetic, benzoic and 1-hydroxy-6-oxocyclohex-2-en-1-carboxylic (HCH) acids. The phenolic

glycosides isolated and/or identified from genus *Salix* are presented in Supplementary Table S2 and Figure 2 .

FIGURE 2

Structures of reported phenolic glycosides from genus *Salix.*

The highest number of phenolic glycosides were reported in *Salix* leaves, followed by twigs, stems and bark. Salicin (141), tremuloidin (164), tremulacin 166) were found to be the major constituents in *S. Acutifolia* Willd. juvenile stem and bark (Zapesochnaya et al., 2002 ; Wu et al., 2016), *S. chaenomeloides* Kimura leaves (Mizuno et al., 1991), *S. glandulosa* Seemen. twigs (Kim et al., 2015) and *S. tetrasperma* Roxb. leaves (El-Shazly et al., 2012).

Some phenolic glycosides were identified as taxonomic markers for different *Salix* species. Acmophyllin A 96) and acmophyllin B 97) identified as taxonomic marker for *S. acmophylla* Boiss. leaves (Shah et al., 2016). Chaenomeloidin (101), cochinchiside A (107), lasiandrin (133), leonuriside A (134), salicin-7-sulfate 152) identified as taxonomic markers for *S. chaenomeloides* Kimura leaves (Mizuno et al., 1991), *S. glandulosa* Seemen. twigs (Kim et al., 2015), *S. lasiandra* leaves and twigs (Reichardt et al., 1992), *S. matsudana* Koidz. leaves (Li et al., 2008) and *S. koriyanagi* Kimura. Stems (Noleto-Dias et al., 2018), respectively. Sachaliside 1 139) and sachaliside 2 (140) were identified as taxonomic markers for *S. sachalinensis* F. Schmidt (Mizuno et al., 1990).

Some *Salix* species were characterized by accumulation of 1, 2-cyclohexanediol glycosides. Compounds (116–128) were detected in *S. glandulosa* Seemen. twigs (Kim et al., 2014). Also, acutifoliside, a benzoic acid derivative 98) was a chemical marker for *S. acutifolia* Willd. juvenile stem (Wu et al., 2016).

Non-Phenolic Glycosides

Non-phenolic glycosides (172, 173, 174, 175, 176, 182–188) were found to be the major constituents in *S. triandra* L. *x dasyclados* Wimmer Wood (Noleto-Dias et al., 2019). Also, compounds (170, 171) are the major constituents in *S. arbusculoides* Andersson twigs (Evans et al., 1995). Some *Salix* species were characterized by accumulation of 1, 2-cyclohexanediol glycosides. Compounds (177, 180) were detected in *S. glandulosa* Seemen. twigs (Kim et al., 2014) and grandidentin 181) was reported in *S. purpurea* L. bark (Pearl and Darling, 1970) (Supplementary Table S3 and Figure 3).

FIGURE 3

Structures of reported non-phenolic glycosides from genus *Salix.*

Organic Acids

Salix species are rich sources for phenolic acids, either in free or esterified form, as benzyl, cinnamyl or phenyl ethyl esters. The aromatic acids are either benzoic or cinnamic acid derivatives: benzoic acid derivatives as *p* -hydroxybenzoic, *p* -anisic, gallic, salicylic, gentisic, vanillic, 2-amino-3-methoxy benzoic and protocatechuic acids, while hydroxycinnamic acid

derivatives as *p* -coumaric, caffeic, isoferuolic, and feruolic acids, (Supplementary Table S4 and Figure 4).

FIGURE 4

Structures of reported organic acids from genus *Salix.*

The higest number of organic acids were detected in *S. purpurea* L., *S. alba* L. bark (Agnolet et al., 2012) which contain compounds (192–194, 198–200, 214), *S. tetrasperma* Roxb. flowers and bark (Sobeh et al., 2019 ; Mostafa et al., 2020) which contain compounds (197, 202, 203, 204, 205–206, 208, 209, 215).

Simple Phenolics

Genus *Salix* comprises a vast variety of simple phenolic compounds (Phenolic acids and their derivatives) (Tuberoso et al., 2011). *S. capensis* Thunb. bark (Masika et al., 2005), *S. acutifolia* Willd. bark (Zapesochnaya et al., 2002), *S. subserrata* Willd. bark (Hussain et al., 2011), *S. caprea* L. inflorescence (Ahmed et al., 2017) were characterized by the accumulation of salicyl alcohol 228) which is the basic nucleus for salicinoids. Also, *S. caprea* L. wood was characterized by the accumulation of different simple phenolics as aucuparin (218), methoxyaucuparin (219), coniferyl alcohol (221), *p* -coumaryl alcohol (222), 4, 2′-dihydroxy-3, 5-dimethoxybiphenyl 223) and sinapylaldehyde 229) (Malterud and Dugstad, 1985 ; Pohjamo et al., 2003), as illustrated in Supplementary Table S5 and Figure 5 .

FIGURE 5

Structures of reported simple phenolics from genus *Salix.*

Sterols and Terpenes

The highest number of sterols and triterpenes was detected in *S. cheilophila* C. K. Schneid. twigs (Shen et al., 2008), *S. tetrasperma* Roxb. bark, leaves and flowers (El-Shazly et al., 2012 ; Sobeh et al., 2019), *S. subserrata* Willd. leaves (Balbaa et al., 1979), *S. denticulate* erial parts (Rawat et al., 2009), *S. babylonica* L. roots (Singh et al., 2017), *S. subserrata* Willd. bark and leaves (Hussain et al., 2011). Whereas phytane and pimarane diterpene were found to be the major constituents in *S. cheilophila* C. K. Schneid. twigs (Shen et al., 2008), as illustrated in Supplementary Table S6 and Figure 6 .

FIGURE 6

Structures of reported sterols and terpenes from genus *Salix.*

Lignans

Sisymbrifolin a lignan derivative 247) had been isolated from the bark of *S. alba* L. (Du et al., 2007) . Recently, pinoresinol (248), lariciresinol (249), secoisolariciresinol (250), 7-hydroxymatairesinol (251), medioresinol (252), and lariciresinol-sesquilignan 253) were detected in the biomass of five willow sp. cultivated in Quebec, Canada (Brereton et al., 2017) as illustrated in Figure 7 .

FIGURE 7

Structures of reported lignans from genus *Salix.*

Volatiles

Terpenes (hemi-, mono- and sesqui-terpenes) and non-terpene (aliphatic, aromatic acids, their esters, carbonyl compounds and hydrocarbons) volatiles were identified in the genus *Salix* . The highest percent of volatiles and fatty acids was reported in *S. caprea* L. inflorescence (Ahmed et al., 2017), and the leaves of *S. egyptiaca* L. (Karimi et al., 2011), *S. babylonica* L. (Salem et al., 2011), and *S. alba* L. (Zarger et al., 2014) (Supplementary Table S7 and Figure 8).

FIGURE 8

Structures of reported volatiles and fatty acids from genus *Salix.*

Traditional Uses

Salix plants have been used medicinally since antiquity and have been linked to the discovery of acetylsalicylic acid and aspirin. These plants had been traditionally used to treat painful musculoskeletal joint pain conditions, inflammation, and fever. Salicin is a major pharmacologically active metabolite in *Salix* and hydrolyzes in the gastrointestinal tract to confer salicyl alcohol and d -glucose. The latter is oxidized, upon absorption, into salicylic acid, the active drug which inhibits cyclooxygenases (COX I, II) (Mahdi, 2010).

S. egyptiaca L (Musk Willow) was important in the Middle East, especially in Iran, as it has been traditionally used to treat anemia and vertigo, as a cardiotonic agent, and also in the preparation of local candies as a fragrance additive (Asgarpanah, 2012). *S. alba* L (white willow), had used in folk

medicine to treat fever, chronic and acute inflammation, pain and infection (Zengion and Yarnell, 2011 ; Maistro et al., 2019). *S. tetrasperma* Roxb. had been used to treat diseases such as epilepsy, diabetes, fever, rheumatism, piles, swellings, stones in bladder, dysentery, wound, ear pain, cough and cold (Prashith Kekuda et al., 2017). *S. alba* L. bark is traditionally used for treatment of flu, rheumatism, fever and headache (Van Wyk and Wink, 2018).

Pharmacological Activity

Different *Salix* species and the isolated compounds as salicylic acid and salicin have been utilized in folk medicine to treat rheumatic diseases, back pain, toothache, headache, and menstrual cramps (Highfield and Kemper, 1999). They exert analgesic, anti-inflammatory, antioxidant, anticancer, cytotoxic, antidiabetic, antimicrobial, anti-obesity, neuroprotective and hepatoprotective activities. The main targets of salicylic acid are cyclooxygenases (COX I, II) which are key enzymes of pathway to prostaglandins which control inflammation and pain. The available scientifically based reports on biological activities of genus *Salix* are summarized in Tables 1 – 8 .

TABLE 1

Anti-bacterial activity of *Salix* species.

TABLE 2

Antifungal, anthelmintic and anti-retroviral activity of *Salix* species.

TABLE 3

Invitro antioxidant activity of *Salix* species.

TABLE 4

In vitro antiproliferative effects of *Salix* species.

TABLE 5

In vivo anticancer effects of *Salix* species.

TABLE 6

In vivo neuroprotective effects of *Salix* species and their major constituents.

TABLE 7

In vivo hepatoprotective effects of *Salix* species and their major constituents.

TABLE 8

In vivo anti-obesity and anti-lipidemic effects of *Salix* species and their major constituents.

Antimicrobial Effects of Salix

Multidrug-resistant bacteria are widely spread, and natural resources have been used as a means of discovering novel antibacterial compounds as they

offer limitless opportunities for the discovery of new agents, particularly against multidrug resistant bacteria.

The main methods used to evaluate the antimicrobial activity of *Salix* extracts are disc diffusion assays, agar well diffusion, broth microdilution methods and the assessment of antibiofilm function (Masika et al., 2005 ; Fayaz and Sivakumaar, 2014 ; Popova and Kaleva, 2015 ; Mostafa et al., 2020). As detailed in Table 1 , microbial growth inhibition zones and percentages along with minimum inhibitory concentrations (MICs) displayed the potential of *Salix* species as substantial antimicrobials and predict their efficacy as functional foods (Mostafa et al., 2020).

Antibacterial Activity

Many previous studies evaluated the antibacterial activity of *Salix* plants and active constituents of their extracts against different types of bacteria such as *Pseudomonas eruginosa* , *Escherichia coli, Staphylococcus aureus* and *Bacillus subtilis* , dental biofilm forming bacteria (*Streptococcus mutans* and *Lactobacillus*), and *Salmonella enterica* (Table 1). Catechol and 2-hydroxybenzyl alcohol derived from the bark of *S. capensis* Thunb. were previously tested for their antibacterial activity. Both compounds exhibited similar antibacterial activity against *P. eruginosa* (Masika et al., 2005). Moreover, *Salix alba* L. bark extract demonstrated antimicrobial activity against the dental biofilm forming bacteria with MIC of 125 µg/ml. Furthermore, it also exhibited a moderate potential against the *Staphylococcus aureus* but the least activity was observed against *E. coli* (Fayaz and Sivakumaar, 2014). Previous studies also showed that the twigs aqueous extract with leaves of *S. babylonica* L. exhibited potent

antimicrobial properties against Gram-negative bacteria (*E. coli* , *Salmonella enterica* , MIC $_{50}$ is 70. 4 ± 17. 41 mg/ml) with a comparable activities to thiamphenicol (The broad spectrum antibiotic). Its effects cover Gram-positive bacteria such as *S. aureus* (Popova and Kaleva, 2015). A recent study performed in our laboratories tested the extracts of both stem bark and flowers of *S. tetrasperma* Roxb. for anti-quorum sensing activity against *Pseudomonas eruginosa* . Both extracts inhibited *P. eruginosa* bacterial growth at 40 mg/ml; however, the bacterial viability was not affected by 1/4 and 1/8 MIC concentrations. When the extracts were tested as anti-quorum sensing agents, they impaired virulence of *P. eruginosa* by declining its swimming and swarming motilities and reducing its hemolytic and proteolytic properties (Mostafa et al., 2020).

Antifungal Activity

Poisoned food technique, broth microdilution method, filter disc assay and growth curve study methods were used to determine the antifungal properties of *Salix* extracts (Table 2). The antifungal activity was evaluated against *Candida guilliermondii* , *C. glabrata* , *C. parapsilosis* and *Fusarium oxysporum* .

Anthelmintic Activity

The anthelmintic potential of *Salix* species to inhibit gastrointestinal and pulmonary parasites in animals was studied. The anthelmintic activity was evaluated against *Ostertagia* , *Moniezia* , *Dictyocaulus, Eimeria* , *Chabertia, Cooperia* , and *Hemonchus contortus* (Table 2). It was reported *Salix babylonica* L (at dose of 20 ml, weekly) was effective against the main parasite species detected in sheep (*Eimeria* spp., *Dictyocaulus* spp., and

Chabertia spp.) more than the most common parasites in goats in southern Mexico farms (*Dictyocaulus* spp. and *Chabertia* spp.) (Salem et al., 2017).

Anti -HIV Activity

Human immunodeficiency virus (HIV) infection that causes acquired immunodeficiency syndrome (AIDs) represents a major health problem worldwide. Chemical anti-retroviral agents are usually used to treat AIDs patients. However, they possess many adverse effects and resistance emerged for many of them. Recently, novel anti-retroviral agents isolated from medicinal plants, played an essential role to replace synthetic drugs. One study investigated the anti-retroviral effects of *S. egyptiaca* L. extract. Results of this study and bioinformatics analyses suggested that the plant had anti-HIV properties and might be a substantial candidate for AIDS patients (Table 2) (Eftekhari et al., 2014).

Antioxidant Activity

Reactive oxygen species (ROS) are associated with several human diseases, such as inflammation, diabetes, ulcers, autoimmune and cardiovascular diseases, viral infections and cancer (Howlett, 2008 ; Rubió et al., 2013 ; Salem et al., 2020). Most of the activities of *Salix* species were attributed to the presence of several polyphenolic with robust antioxidant activities (Table 3). The antioxidant effects of *Salix* extracts and their flavonoids were mainly assessed by DPPH, ABTS, FRAP, total antioxidant capacity (TAC) assays, Folin-Ciocalteu method, β-carotene bleaching, lipid peroxidation capacity, inhibition of linoleic acid oxidation, superoxide anion radical scavenging, and alkyl radical scavenging assays (Ceyhan, 2014; Gawlik-Dziki et al., 2014; Tavakoli et al., 2016; Zaiter et al., 2016; Nauman et al., 2018;

Zabihi et al., 2018; Gligoric' et al., 2019). A recent study from our lab investigated the possible effect of *S. tetrasperma* Roxb. extract on neuropathic pain and its mechanism of action showed a potent *in vitro* and *in vivo* antioxidant effects (Sobeh et al., 2019). Furthermore, *S. atrocinerea* Brot. , *S. fragilis* L. and *S. viminalis* L. showed antioxidant effects mediated by their polyphenolic contents (Ramos et al., 2019). Another study from our laboratory showed that *S. subserrata* Willd. leaf extracts contained isorhamnetin-3- *O* - *β* - d -rutinoside, triandrin, gallocatechin, tremuloidin, aromadendrin, salicin, and chrysoeriol-7- *O* -glucuronid and exerted antioxidant effects against oxidative stress in *Caenorhabditis elegans* (Tawfeek et al., 2019).

Anti-Inflammatory Activity

Inflammation is a frequent condition because of exposure to different stimuli including microbial infection and wounding. It decreases the spread of infection, followed by resolution and the restoration of normal structural and functional of affected tissues (Nathan and Ding, 2010). However, non-resolving inflammation contributes significantly to the pathogenesis of many diseases such as atherosclerosis, obesity, cancer, and inflammatory bowel disease. *Salix* extracts exert potent anti-inflammatory effects that are responsible for many biological effects. The hydroalcoholic extract of *S. tetrasperma* Roxb. in two dose levels (100 and 200 mg/kg) demonstrated anti-inflammatory effects in carrageenan induced rat paw edema model (Kishore et al., 2014). We showed previously that the flower extract of *S. tetrasperma* Roxb. has analgesic, antipyretic, and anti-inflammatory effects against carrageenan induced vascular permeability and carrageenan induced

hind paw edema. It inhibited COX-1, COX-2 and LOX and suppressed elevated levels of TNF-a and NF-κB in chronic neuropathic pain model (Sobeh et al., 2019). Oral administration of *S. canariensis* extract significantly decreased writhing, moderately reduced formalin-induced pain and showed a promising dose-dependent anti-inflammatory activities. These effects were attributed to the presence of pentacyclic triterpenes and polyphenolics (Gutiérrez et al., 2017). An early study showed that *S. caprea* L. is a potent cyclooxygenase inhibitor (Tunon et al., 1995). Another study showed that S. *subserrata* Willd. and *S. tetrasperma* Roxb. showed anti-inflammatory effects against carrageenan induced hind paw edema due to the presence of phenolic glycosides mainly salicin as well as the flavonoids luteolin, quercetin and rutin (Karawya et al., 2010). *S. matsudana* Koidz. leaves methanol extract also showed significant inhibitory activities against cyclooxygenases (COX-1 and COX-2) due to the presence of matsudone, luteolin 7-O-glucoside and 4′, 7-dihydroxyflavone (Li et al., 2008).

Anticancer Activity

There are several risk factors that can increase the development of cancer that have a basis of low-grade inflammation and oxidative stress. Therefore, targeting inflammatory pathways and suppressing oxidative stress may contribute to inhibition of initiation, proliferation and even cancer metastasis and subside resistance to chemotherapy and radiation. *Salix* extracts, by possessing both anti-inflammatory and potent antioxidant potential, are promising natural sources in fighting cancer. The antiproliferative activities of *Salix* extracts were determined by cell viability percentages and IC_{50} values using several *in vitro* assays. The most commonly utilized cancer cell

lines were human acute lymphoblastic leukemia (ALL cells), human acute myeloid leukemia cells (AML cells), PC3 cells (Prostate cancer cells), Hep G2 cells (Liver cancer cells), HCT116 (Colorectal cancer cells), MCF7 (Breast cancer cells), HT-29 and HCT 116 (human colon COX-2 positive and negative cells respectively), A549, SW2 cells, and human lung cancer cell line (H1299).

It was observed that a fraction of *Salix* extracted by non-polar solvents such as (petroleum ether, ether, and chloroform) has the minimum killing potential against AML cells while fraction extracted by polar solvents such as 70% ethanol and water has major destructive effect on AML cells (El-Shemy et al., 2003). Thus, *Salix* cytotoxic activity could be attributed to the polyphenolics, tannins, and glycosides, that are commonly dissolved in water or ethanol solutions including salicin and saligenin. When salicin is tested against leukemic cells it caused destruction of myeloblasts by 70–75%. Eight compounds isolated from *S. hulteni* Flod (1-p-coumaroyl-β-D-glucoside, aromadendrin, catechin, 4-hydroxyacetophenone, picein, sachaliside 1, naringenin and dihydromyricetin) were tested for their cytotoxic potential against brine shrimp and a human lung cancer cell line (H1299). Naringenin, aromadendrin, catechin, and 1- *p* -coumaroyl-β-D-glucoside showed mild cytotoxic activity, with dihydromyricetin showing the strongest cytotoxic effects. 4-Hydroxyacetophenone, picein, and sachaliside one did not show a significant cytotoxic activity indicating that flavonoid compounds are responsible for the cytotoxic effects of *S. hulteni* Flod. (Jeon et al., 2008). Brine shrimp lethality test is commonly used to test cytotoxic effects of natural products. The methanol extract of *S. nigra* exerted concentration

dependent cytotoxic effects against brine shrimp indicating promising cytotoxic effects (Ahmed et al., 2016). Willow bark extract (A pharmaceutically used extract BNO 1455) and its fractions (flavonoids, proanthocyanidins, salicyl alcohol derivatives) showed dose dependent cytotoxic effects against human colon and lung cancer irrespective of their COX-2 selectivity (Hostanska et al., 2007). *S. caprea* L. exerted a protective effect against phorbol ester induced skin tumor promotion when applied to the skin of mice prior to the application of phorbol ester. Anti-tumor activity of *S. caprea* L. may be attributed to potent antioxidants constituents of *S. caprea* L. such as luteolin, dihydrokaempferol and quercetin (Sultana and Saleem, 2004).

Neuroprotective Effect

Only few studies investigated the effect of *Salix* species on central and peripheral nervous system. Virupaksha et al. (2016) investigated the effects of *S. tetrasperma* Roxb. leaf extract on locomotor activity and muscle relaxant activity. They demonstrated that the extract decreased locomotor activity indicating central nervous system (CNS) depressant activity and induced a decrease in fall off time due to loss of muscle grip implying skeletal relaxation (Virupaksha et al., 2016). The CNS depressant activity of the extract was attributed to binding of flavonoids to gamma-aminobutyric acid (GABA) receptors in the CNS (Hossain et al., 2009). Another study from our laboratory investigated the possible protective effect of *S. tetrasperma* Roxb. on neuropathic pain model, chronic constriction injury of sciatic nerve model. In this work, we explored the effects of the extract on central and peripheral nervous system in this model. We showed that the extract

improved hyperalgesia and allodynia, the major signs of neuropathic pain through inhibition of oxidative stress and inflammation in sciatic nerve and brain stem (Sobeh et al., 2019).

Hepatoprotective Effects

S. subserrata Willd. flower extract showed marked hepatoprotective effects mostly through lowering the elevated liver enzymes and decreasing the protein levels of two inflammatory biomarkers (NF-κB and TNF-α) in carbon tetrachloride (CCl_4)-induced liver damage model (Wahid et al., 2016). It also presented a remarkable ability to reduce lipid peroxidation and had antioxidant effects related to several active ingredients that include flavonoids such as quercetrin, luteolin-7-glucoside, rutin, and quercetin and phenolic compounds such as salignin and catechins.

Anti-Obesity and Anti-lipidemic Effects

As shown in Table 8 , remarkable anti-obesity and anti-lipidemic effects have been attributed to *Salix* extracts. The reduction of parametrial adipose tissue weight and body weight gain, the reduction of liver total cholesterol contents and inhibition of the elevated blood triacylglycerol are among the most prominent, directly attributed to its ability to inhibition of intestinal absorption of dietary fat (Liu, 2012). These effects have been mostly attributed to polyphenol fractions (apigenin-7- *O* -D-glucoside, luteolin- *O* -D-glucoside and chrysoeriol-7- *O* -D-glucoside) which inhibited palmitic acid incorporation into small intestinal brush border membrane vesicles (Han et al., 2003). It was reported that methanol extract of *S. pseudo-lasiogyne* H. Lév. twigs and salicortin derivatives reduced lipid accumulation in a concentration-dependent manner. They inhibited the differentiation of

adipocytes in 3T3-L1 cells. The 2′, 6′- *O* -acetylsalicortin exhibited the most potent inhibitory activity with IC_{50} = 11. 6 μM. It remarkably downregulated the expressions of sterol regulatory element binding protein 1 (SREBP1c) and CCAAT/enhancer binding protein α (C/EBPα). Thus, salicortin derivatives possessed anti-adipogenic effects via down-regulation of SREBP1c and C/EBPα dependent pathways (Lee et al., 2013).

Conclusion and Future Perspectives

The current review outlined the complete research progress in the phytochemistry, traditional use and pharmacology of genus *Salix* plant extracts and constituents. *Salix* extracts and some of its components exerted potent antioxidant, anti-inflammatory, antiproliferative, and antimicrobial properties confirming the traditional use of willow extracts in folk medicine. They also demonstrated substantial abilities in suppressing inflammatory pathways, both in cancer prevention and treatment, and in other chronic diseases. Thus, as a potential perspective, *Salix* extracts alone or their isolated active components should be examined more thoroughly, and its anti-HIV, hepatoprotective and neuroprotective therapeutic approach should also be discussed.

Author Contribution

NT retrieved the relevant literature and drafted the manuscript. AME and MW originated the work, led the discussions, provided helpful comments, and revised the manuscript. MF wrote the biological activity part. DH, MS and NF provided helpful comments and revised the manuscript. All authors read and approved the final version of the manuscript.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary Material

The Supplementary Material for this article can be found online at: https://www. frontiersin. org/articles/10. 3389/fphar. 2021. 593856/full#supplementary-material .

Glossary

ABTS2, 2′-azinobis-(3- ethylbenzothiazoline-6-sulfonic acid)

AIDsAcquired immunodeficiency syndrome

ApifApiofuranosyl

ArafArabinofuranosyl

ArapArabinopyranosyl

CCl_4 Carbon tetrachloride

C/EBPαCCAAT/enhancer binding protein α

DPPH2, 2-Diphenyl, one- Picryl Hydrazyl

EACCEhrlich ascites carcinoma cells

EtOAcEthyl acetate

FRAPFerric reducing antioxidant power

GlacGalactosyl

GlcGlucosyl

GlucGlucuronoyl

HexHexosyl

HFDHigh-fat diet

HIVHuman immunodeficiency virus

IC_{50} Half maximal inhibitory concentration

MeOHMethanol

MICMinimal inhibitory concentration

NF-κBNuclear factor kappa-B

ORACOxygen radical absorbance capacity

PentPentosyl

PhPhenyl

RhRhamanosyl

RutRutinosyl

SREBP1cSterol regulatory element binding protein 1

TACTotal antioxidant capacity

TFCTotal flavonoid content

TLCThin layer chromatography

TNF-α: Tumor necrosis factor-alpha

TPCTotal phenolic content

XTT2, 3-bis-(2-methoxy-4-nitro-5-sulfophenyl)-2H- tetrazolium-5-carboxanilide

XylpXylopyranosyl.

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