Phytochemistry, Pharmacology and Medicinal Uses of Plants of the Genus Salix: An Updated Review

Nora Tawfeek1,2, Mona F. Mahmoud3, Dalia I Hamdan4, Mansour Sobeh1,5, Nawaal Farrag2, Michael Wink1* and Assem M. El-Shazly2*

1Institute of Pharmacy and Molecular Biotechnology, Heidelberg University, Heidelberg, Germany, 2Department of Pharmacognosy, Faculty of Pharmacy, Zagazig University, Zagazig, Egypt, 3Department of Pharmacology and Toxicology, Faculty of Pharmacy, Zagazig University, Zagazig, Egypt, 4Department of Pharmacognosy, Faculty of Pharmacy, Menoufia University, Shibin Elkom, Egypt, 5AgroBioSciences Research Division, Mohammed VI Polytechnic University, Ben-Guerir, Morocco

The Willows (genus Salix), with more than 330–500 species and 200 hybrids, are trees, shrubs or prostrate plants that are widely distributed in Africa, North America, Europe, and Asia. The genus is traditionally used in folk medicine and represents a valuable source of biologically active compounds among them salicin, a prodrug for salicylic acid. Altogether, 322 secondary metabolites were characterized in the genus including flavonoids (94) (flavonols, flavones, flavanones, isoflavones, flavan-3-ols (catechins and procyanidins), chalcones, dihydrochalcone, anthocyanins, dihydroflavonols), phenolic glycosides (76), organic acids (28), and non-phenolic glycosides (17), sterols and terpenes (17), simple phenolics (13) and lignans (7) in addition to volatiles and fatty acids (69). Furthermore, willows exert analgesic, anti-inflammatory, antioxidant, anticancer, cytotoxic, antidiabetic, antimicrobial, antiobesity, neuroprotective and hepatoprotective activities. The current review provides an updated summary of the importance of willows, their chemical composition and pharmacological activities.

Keywords: salix, phytochemistry, pharmacology, medicinal and traditional uses, inflammation

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 amenotiferous (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 canning, 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

![Figure 1: Structures of reported flavonoids from the genus *Salix*.](image)
FIGURE 1 (Continued).
\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure1}
\caption{(Continued).}
\end{figure}

\begin{table}
\centering
\begin{tabular}{ccc}
\hline
No. & \(R_1\) & \(R_2\) & \(R_3\) \\
\hline
48 & OH & OH & OH \\
49 & \(\text{OSO}_3\text{H}\) & OH & OH \\
50 & OH & \(\text{O-Glc.}\) & OH \\
51 & OH & OH & H \\
52 & \(\text{OSO}_3\text{H}\) & OH & H \\
53 & \(\text{O-Glc.}\) & OH & H \\
54 & OH & \(\text{O-Glc.}\) & H \\
55 & \(\text{O-(6''-trans-p-Coumaroyl) glucosyl}\) & OH & H \\
\hline
\end{tabular}
\end{table}

\begin{table}
\centering
\begin{tabular}{ccc}
\hline
No. & \(R_1\) & \(R_2\) & \(R_3\) \\
\hline
56 & OH & OH & OH \\
57 & OH & H & H \\
58 & \(\text{OSO}_3\text{H}\) & H & H \\
59 & OH & OH & H \\
60 & \(\text{OSO}_3\text{H}\) & OH & H \\
61 & \(\text{OCH}_3\) & OH & H \\
62 & \(\text{OCH}_3\) & \(\text{O-Glc.}\) & H \\
\hline
\end{tabular}
\end{table}
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; Polocka-Olech and Krauze-Shao et al., 1989; Du et al., 2004; Zeid, 2006; Jürgenliemk 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.

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 (Khatooe 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 leaves (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 aerial 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

![Chemical structures](image-url)
FIGURE 2 | Structures of reported phenolic glycosides from genus Salix.
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. and 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.
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). Chaenomeloiadin (101), cochiniside 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).

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).

The highest 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 (Sobei et al., 2019), *M. 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. subserata* 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.

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; Sobei et al., 2019), *S. subserata* Willd. leaves (Balbaa et al., 1979), *S. denticulate* erial parts (Rawat et al., 2009), *S. babylonica* L. roots (Singh et al., 2017), *S. subserata* 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.
Lignans
Sisymbriifolin 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.

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. in fluorescence (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).

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.

**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 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 (Eimeriaspp., 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. egypitaca 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

![FIGURE 6 | Structures of reported sterols and terpenes from genus Salix.](image-url)
antioxidant capacity (TAC) assays, Folin-Ciocalteu method, \( \beta \)-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 \textit{S. tetrasperma} Roxb. extract on neuropathic pain and its mechanism of action showed a potent \textit{in vitro} and \textit{in vivo} antioxidant effects (Sobeh et al., 2019). Furthermore, \textit{S. atrocinerea} Brot., \textit{S. fragilis} L. and \textit{S. viminalis} L. showed antioxidant effects mediated by their polyphenolic contents (Ramos et al., 2019). Another study from our laboratory showed that \textit{S. subserrata} Willd. leaf extracts contained isorhamnetin-3-O-\( \beta \)-d-rutinoside, triandrin, gallocatechin, tremuloidin, aromadendrin, salicin, and chrysoeriol-7-O-glucuronid and exerted antioxidant effects against oxidative stress in \textit{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. subserata* 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

**FIGURE 8** | Structures of reported volatiles and fatty acids from genus *Salix.*
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. hultenii 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. hultenii 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...
P. aeruginosa
Methanol extracts of
monocytogenes
Listeria
S. aureus
E. coli,
enterica
Salmonella
E. coli
sp
Lactobacillus
S. aureus
S. mutans
P. aeruginosa
E. coli
S. aureus
B. subtilis
Bacteria
Extract/Compound
Used method
Effects
References

Virus
Strongiloides
Dictyocaulus,
Eimeria
Parasites
Fungi
Candida guilliermondii, C. glabrata and C. parapsilosis
Ethanol extract of S. babylonica L. root
Poisoned food technique
Good fungicidal activity at 20% concentration
Sati et al. (2013)

C. parapsilosis
Methanol extract of S. albica L. leaves
Poisoned food technique
MIC = 800 μg/ml, 800 μg/ml and 1,600 μg/ml respectively. Inhibition i.e. 12 mm for C. glabrata followed by 11 mm measured in C. parapsilosis. C. guilliermondii inhibition was 10 mm
Zarger et al. (2014)

Parasites
Hemonchus contortus,
Eimeria
Cooperia, Chabertia,
Dictyocaulus,
Moniezia, and Ostertagia
Bonostomum sp.,
Strongaloides papillosus, and Nematodruss pathiger
Nematodruss battus

Micro-organism
Extract/compounds
Used method
Effects
References

HIV-1
S. egyptiaca L. Pr
extract
XTT method. Inhibition of p24 Ag production level assay
The IC50 in HeLa infected cells was 45 μg/ml 100 μg/ml extract inhibited the production of HIV-1 p24 Ag by more than 80%
Effekhari et al. (2014)

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...
## TABLE 3 | In vitro antioxidant activity of *Salix* species.

| Plant part                  | Extract/compound                                                                 | Method                                       | Effects                                                                 | References                                      |
|-----------------------------|----------------------------------------------------------------------------------|----------------------------------------------|------------------------------------------------------------------------|------------------------------------------------|
| Stem and leaves             | Four sulfated flavonoids (taxifolin-7-sulfate, dihydrokaempferol-7-sulfate, eriodictyol-7-sulfate and rhamnetin-7-sulfate) isolated from hybrid species of *Salix alba* | DPPH                                         | 7-Sulfation of taxifolin and eriodictyol attenuated but does not remove antioxidant activity | Noleto-Dias et al. (2020)                        |
| Leaves                     | Ethanolic extracts of *S. purpurea*, *S. cinerea*, *S. alba*, *S. eriocephala* and *S. rubra* | DPPH                                         | The scavenging effect ranged between 33.6 (S. purpurea L.) and 45.7% (S. cinerea L.), 50.7 (S. purpurea L.) to 56.3% (S. rubra L.) | Gasecka et al. (2017)                           |
| Leaves                     | Ethyl acetate extract of *S. tetrasperma* roxb.                                | DPPH assay                                   | IC₅₀ = 65.89 µg/ml                                                      | Januario et al. (2019)                          |
| Leaves                     | Methanol extract of *S. mucronata andersonn*                                   | DPPH, ABTS and TAC assays                   | DPPH (EC₅₀ = 98.76 ± 0.46 (µg/ml), ABTS = 45.83 ± 0.32, trolox eq./100 gm extract and TAC = 199.18 ± 2.19 mg equivalent of ascorbic acid/g extract) | Alam et al. (2008)                             |
| Male inflorescence         | Methanol extract of *S. egyptiaca*                                              | DPPH and the folin-Ciocalteu method          | Butanol fraction showed the highest antioxidant potential with an IC₅₀ value of 27.7 µg/ml | Sonboli et al. (2010)                          |
| Flowers                    | Ethanol extract of *S. caprea*                                                   | DPPH, superoxide hydrogen peroxide and nitric oxide scavenging assay | At a concentration of 250 µg/ml, 85.04% of DPPH radicals and at µg/mL 45.97%, 17.97% and 56.53% of O₂, H₂O₂ and NO, respectively, were scavenged by the *S. caprea* L. flower extract | Enayat and Banerjee (2009)                      |
| Leaves, bark, catkins      | Cyclohexane, butanol, ethanol and water extracts of *S. egyptiaca*              | DPPH assay                                   | Ethanol extract of the bark (highest activities, IC₅₀ = 19 µg/ml)        | Sulaiman et al. (2013)                         |
| Bark                       | Hot ethanol extract of *S. alba*                                                 | DPPH and folin-ciocalteu method              | Free radical scavenging activity values ranged between 125, 37.50 and 80.00% of 10, 50 and 100 µg/mL, respectively | Gawlik-Dziki et al. (2014)                      |
| Bark                       | *S. alba* L., *S. daphnoides* VII, *S. purpurea* L., and *S. daphnoides* VII x pupurea L. hybrid willow clones | ABTS                                         | S. daphnoides VII x purpurea L. extracts were the most active ones.    | Zabihi et al. (2018)                           |
| Leaves and young stems     | Hydroethanolic extract of *S. alba* L.                                          | DPPH                                         | IC₅₀ = 19.1 µg/ml                                                       | Tavakoli et al. (2016)                         |
| Leaves and male inflorescence catkin | *S. matsudana* Koidz., *S. aegyptiaca* L., *S. babylonica* L., *S. excelsa* G. Koidz., and *S. acmophylla* Boiss. | DPPH, superoxide, nitric oxide and hydrogen peroxide radical scavenging activity | DPPH results ranged from 40.08% (S. excelsa) to 91.94% (S. aegyptiaca L.) and *S. excelsa* G. Koidz. displayed the potent superoxide (99.00%) and nitric oxide (71.73%) scavenging potential. Similar activities were found for hydrogen peroxide radical scavenging (50%) for *S. matsudana* Koidz., *S. acmophylla* Boiss., *S. babylonica* L., Male inflorescence catkin extracts, S. excelsa G. Koidz (70.63%), S. acmophylla Boiss. (80.25%) and S. matsudana Koidz. (82.37%) presented the most activities in DPPH, nitric oxide and hydrogen peroxide, respectively. The S. excelsa S. G. Koidz, S. aegyptiaca L. and S. babylonica L. showed 99% superoxide radical inhibition. | Ceyhan (2014)                                    |
| Bark                       | Gallic acid, quercetin, rutin, vanillin and acetylsalicylic acid obtained from *S. aegyptiaca* L. | DPPH                                         | gallic acid > quercetin >rutin > vanillin > acetylsalicylic acid.      | Nauman et al. (2018)                           |
| Bark                       | Ethanolic extract of *S. aegyptiaca* L.                                         | DPPH                                         | Ethyl acetate fraction showed the highest activity (11 ± 1 µg/ml).      | Ceyhan (2014)                                    |

(Continued on following page)
Leaves and bark n-Hexane, dichloromethane, ethyl acetate and S. alba bark and leaves from our laboratory investigated the possible protective effect of stress and in the major signs of neuropathic pain through inhibition of oxidative We showed that the extract improved hyperalgesia and allodynia, the extract on central and peripheral nervous system in this model. In this work, we explored the effects of tetrasperma injury of sciatic nerve model. In this work, we explored the effects of S. subserrata Willd. Hepatoprotective Effects (GABA) receptors in the CNS (Hossain et al., 2009). Another study et al. (2003) showed that the activity of the extract was mostly through lowering the elevated blood triacylglycerol are among the most

| Plant part | Extract/compound | Method | Effects | References |
|------------|------------------|--------|---------|------------|
| Bark       | S. alba L.       | DPPH   | All granulometric classes revealed a high antioxidant activity. The best results were obtained for the 50–100 μM granulometric class. | Zaiter et al. (2016) |
| Flowers    | Methanol extract of S. tetrasperma Roxb | TAC    | 30.97 ± 2.6, 26.8 ± 2.1 U/L for the extract and ascorbic acid, respectively. | Sobeh et al. (2019) |
| Bark       | S. atrocinaea Brot., S. fragilis L., and S. viminalis L. bark polar extracts | DPPH and ABTS. | Strong free radical scavenging activity (5.58–23.62 μg mL⁻¹ IC50 range. | Ramos et al. (2019) |
| Leaves and bark | n-Hexane, dichloromethane, ethyl acetate and n- butanol extracts of S. subserrata Willd. | DPPH and FRAP assays. | IC50 of DPPH ranged from 1.83–7.79 μg/mL in bark and 1.95–8.07 μg/mL in leaves extracts of different species of the genus Salix | Gligorić et al. (2019) |
| bark and leaves | S. alba L., S. amplexicaulis Bory & Chab., S. babylonica L., S. eleagnos Scop., S. fragilis L., S. purpurea L. and S. triandra. L. | DPPH and OH radical scavenging assay. | | |

| Extract/compound | Cell line | Methods | Results | Mechanism of | References |
|------------------|-----------|---------|---------|--------------|------------|
| Aqueous extract from S. safsaf forsk | Human colon cyclooxygenase-2 (COX-2)-positive HT 29 and (COX-2)-negative HCT 116 or lung COX-2 proficient a 549 and low COX-2 expressing SW2 cells | WST-1 assay and propidium iodide uptake by flow cytometry, annexin V adhesion using flow cytometry for apoptosis | Cells are killed through denaturation of some enzymes and proteins that are induced by salicin and saligenin | | |
| Aqueous extract of leaves extract of S. safsaf forsk. Salicin and saligenin | AML, ALL | Trypan blue exclusion test | Killed most of the blasts of acute myeloid leukemia (AML, 73.8%) | | |
| Salicyalcohol derivatives, flavonoids, proanthocyanidins, and salicyl isolated from willow bark extract BNO 1455 | Human colon cyclooxygenase-2 (COX-2)-negative HT 29 and (COX-2)-positive HT 29 | Trypan blue exclusion test | A remarkable destruction of lymphoblasts (75%) was observed after 24 h incubation of the mononuclear ALL cells with extract. Similar trends were observed for mononuclear AML cells. The mean viability of willow extract treated cells was 26.2% | | |

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 (CCL4)-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 quercetin, 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

| Table 4 | In vitro antiproliferative effects of Salix species. |
|------------------|------------------|---------|---------|--------------|------------|
| Extract/compound | Cell line | Methods | Results | Mechanism of | References |
|------------------|-----------|---------|---------|--------------|------------|
| Aqueous extract from S. safsaf forsk | AML | Trypan blue exclusion test | Killed most of the blasts of acute myeloid leukemia (AML, 73.8%) | Cells are killed through denaturation of some enzymes and proteins that are induced by salicin and saligenin | B-Shemy et al. (2003) |
| Aqueous extract of leaves extract of S. safsaf forsk. Salicin and saligenin | ALL and AML | Trypan blue exclusion test | A remarkable destruction of lymphoblasts (75%) was observed after 24 h incubation of the mononuclear ALL cells with extract. Similar trends were observed for mononuclear AML cells. The mean viability of willow extract treated cells was 26.2% | Unknown receptors on the surface of leukemic cells may be binding with Salix extract compounds and leading to DNA destruction | B-Shemy et al. (2007) |
| Salicyalcohol derivatives, flavonoids, proanthocyanidins, and salicyl isolated from willow bark extract BNO 1455 | Human colon cyclooxygenase-2 (COX-2)-positive HT 29 and (COX-2)-negative HCT 116 or lung COX-2 proficient a 549 and low COX-2 expressing SW2 cells | WST-1 assay and propidium iodide uptake by flow cytometry, annexin V adhesion using flow cytometry for apoptosis | Glu3; 33.3–102.3 μg/ml for flavonoids and proanthocyanidins fractions and 50.0–243.0 μg/ml for salicyl alcohol derivatives and extract | ND | Hostanska et al. (2007) |
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-7-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-acetyl-salicortin exhibited the most potent inhibitory activity with IC₅₀ = 11.6 μM. It remarkably downregulated the expressions of sterol regulatory element binding protein

| TABLE 5 | In vivo anticancer effects of Salix species. |
| Extract/compound | Doses | Route of administration | Methods | Effects | Mode of action | References |
|-------------------|-------|-------------------------|---------|--------|---------------|------------|
| Aqueous extract from the young developing leaves of willow (S. safsaf forsk.) | 0.2 and 0.6 ml of extract (10% w/v) | Oral EACC were injected into the intraperitoneal cavity of mice | The willow extract reduced the tumor growth and delayed the death was delayed | Promote apoptosis, cause DNA damage, and affect cell membranes and/or denature proteins | El-Shemy et al. (2007) |
| Acetone soluble fraction of S. caprea L. flowers | 0.5, 1.0 and 1.5 mg/kg | Topical application on the skin | 7,12-Dimethyl benz[a]anthracene DMBA-initiated croton oil (phorbol ester)mice | Reduction in tumor incidence and number of tumors per mouse ranging from 20 to 50% and 50–63% | Intercep the free radicals and protect cellular macromolecules from oxidant damage. Effectiveness in inhibiting the ornithine decarboxylase activity and maintaining the activity of phase II enzymes after toxicant exposure | Sultana and Saleem (2004) |

| TABLE 6 | In vivo neuroprotective effects of Salix species and their major constituents. |
| Extract/Compound | Doses | Route | Model | Effect | References |
|-------------------|-------|-------|-------|--------|------------|
| Ethanol and aqueous extracts of S. tetrasperma roxb. Leaves | 200 and 400 mg/kg | Oral | Mice | Decrease locomotor activity indicating CNS depressant activity in mice and has muscle relaxant activity | Virupaksha et al. (2016) |
| Methanol extract of S. tetrasperma roxb. Flowers | 200 and 400 mg/kg | Oral | CCI rat model | Relieve hyperalgesia and allodynia responses | Sobeh et al. (2019) |

| TABLE 7 | In vivo hepatoprotective effects of Salix species and their major constituents. |
| Extract/Compound | Doses | Route | Model | Effect | References |
|-------------------|-------|-------|-------|--------|------------|
| Ethanol extract of S. subserrata willd. Leaves | 150 mg/kg | Oral | CCl4-induced chronic hepatotoxicity in rats | The elevated serum levels of intracellular liver enzymes and the expression levels of TNF-α and NFRs proteins were reduced | Wahid et al. (2016) |
| S. caprea L. flowers | 50, 100, 150 mg/kg | Oral | Mice injected with ferric nitritotriacetate (FeNTA) | Decreased hepatic lipid peroxidation, increased hepatic glutathione (GSH) content and the activities of antioxidant enzymes (catalase (CAT), glutathione reductase (GR) and glutathione peroxidase) | Alam et al. (2006) |

| TABLE 8 | In vivo anti-obesity and anti-lipidemic effects of Salix species and their major constituents. |
| Extract/compound | Doses | Route of administration | Model | Effects | References |
|-------------------|-------|-------------------------|-------|--------|------------|
| Ethanol extracts prepared from S. babylonica L. leaves | 2.5 or 10 g (extract/kg food) 10% | Supplemented in diet | HFD mice | Decreased body weight and parametrial adipose tissue weight | Liu (2012) |
| Ethanol extracts prepared from S. babylonica L. leaves | | Supplemented in diet | Rats orally administered 1 ml of a lipid emulsion composed | The extracts inhibited the elevation of blood triacylglycerol | Liu (2012) |
| Polyphenol fractions of S. matsudana koditz. Leaves | 5% | Supplemented in diet | HFD mice | Decreased body weight and reduced the hepatic total cholesterol content | Han et al. (2003a) |
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.

REFERENCES

Agnolet, S., Wiese, S., Verpoorte, R., and Staerk, D. (2012). Comprehensive analysis of commercial willow bark extracts by new technology platform: combined use of metabolomics, high-performance liquid chromatography–solid-phase extraction–nuclear magnetic resonance spectroscopy and high-resolution radical scavenging assay. J. Chromatogr. A. 1262, 130–137. doi:10.1016/j.chroma.2012.09.013

Ahmed, A., Akbar, S., and Shah, W. A. (2017). Chemical composition and pharmacological potential of aromatic water from Salix caprea inflorence. Chin. J. Integr. Med. 1–5. doi:10.1007/s11655-017-2781-5

Ahmed, W., Ahmad, M., Khan, R. A., and Mustaq, N. (2016). Promising inhibition of krait snake’s venom acetylcholinesterase by Salix nigra and its role as an anticancer, antioxidant agent. Indian J. Anim. Res. 50, 317–323. doi:10.18805/ijar.10711

Alam, M. S., Kaur, G., Jabbar, Z., Javed, K., and Athar, M. (2006). Evaluation of antioxidant activity of Salix caprea flowers. Phytother. Res. 20, 479–483. doi:10.1002/tr.1882

Argus, G. W. (2006). Guide to the identification of salix (willow) in Illinois, Indiana, Ohio, and Pennsylvania. Ottawa, Ontario: Canadian Museum of Nature, 47.

Argus, G. W. (2007). Salix (Salicaceae) distribution maps and a synopsis of their classification in North America, North of Mexico. Harv. Pap. Bot. 12, 335–368. doi:10.3100/1043-4534/2007[12][335ssdmaa].2.0.co;2

Asgarpanah, J. (2012). Phytopharmacology and medicinal properties of Salix aegyptiaca L. Afr. J. Biotechnol. 11, 7145–7150. doi:10.5897/AJB12.418

Balbaa, S., Khafagy, S., Haggag, M., and Sahsah, N. (1979). Phytochemical study of certain Salix species cultivated in Egypt. J. Pharmacol. Sci. 20, 153–164.

Binns, W. W., Blunden, G., and Woods, D. L. (1968). Distribution of leucoanthocyanidins, phenolic glycosides and imino-acids in leaves of Salix species. Phytochemistry 7, 1577–1581. doi:10.1016/s0031-9422(00)88090-4

Brereton, N. J. B., Berthod, N., Lafleur, B., Pedneault, K., Pitre, F. E., and Labrecque, M. (2017). Extractable phenolic yield variation in five cultivars of mature short rotation coppice willow from four plantations in Quebec. Ind. Crop. Prod. 97, 525–535. doi:10.1016/j.indcrop.2016.12.049

Bridle, P., Stott, K. G., and Timberlake, C. F. (1970). Anthocyanins in salix species. Phytochemistry 9, 1097–1098. doi:10.1016/s0031-9422(00)85231-0

Bridle, P., Stott, K. G., and Timberlake, C. F. (1973). Anthocyanins in Salix species: a new anthocyanin in Salix purpurea bark. Phytochemistry 12, 1103–1106. doi:10.1016/0031-9422(73)85023-x

Ceyhan, M. S. (2014). Investigation of antioxidant properties and anticarcinogenic effects of Ethanolic extract from bark of Salix aegyptiaca and its fractions. MS thesis. Ankara, Turkey: Middle East Technical University.

Christenhusz, M. J. M., and Byng, J. W. (2016). The number of known plants species in the world and its annual increase. Phytotaxa. 261, 201–217. doi:10.11646/phytotaxa.261.3.1

Du, Q., Jerz, G., Shen, L., Xiu, L., and Winterhalter, P. (2007). Isolation and structure determination of a lignan from the bark of Salix alba. Nat. Prod. Res. 21, 451–454. doi:10.1080/14786410601083845

Du, Q., Jerz, G., and Winterhalter, P. (2004). Preparation of three flavonoids from the bark of Salix alba by high-speed countercurrent chromatographic separation. J. Liq. Chromatogr. Relat. Technol. 27, 3257–3264. doi:10.1081/jlc-200034917

Eftekhari, Y., Rustaiyan, A., Monajemi, M., and Khavari-nejad, R. A. (2014). Study of anti-retroviral effects of Salix aegyptiaca L. herbal extract on HIV-1 in vitro. Int. J. Mol. Clin. Microbiol. 1, 398–405.

El-Sayed, M. M., El-Hashash, M. M., Mohamed, H. R., and Abdel-Lateef, E. E.-S. (2015). Phytochemical Investigation and in vitro antioxidant activity of different leaf extracts of Salix mucronata Thunb. J. Appl. Pharmaceut. Sci. 5, 080–085. doi:10.7324/japs.2015.501213

El-Shazly, A., El-Sayed, A., and Fikrey, E. (2012). Bioactive secondary metabolites from Salix tetrasperma Roxb. Z. Naturforsch. C. Biosci. 67, 353–359. doi:10.5560/znc.2012.67.0353

El-Semy, H. A., Aboul-Enein, A. M., Aboul-Enein, K. M., and Fujita, K. (2007). Willow leaves’ extracts contain anti-tumor agents effective against three cell types. PloS One 2, e178. doi:10.1371/journal.pone.0000178

El-Shemy, H. A., Aboul-Enein, A. M., Aboul-Enein, M. I., Issa, S. I., and Fujita, K. (2003). The effect of willow leaf extracts on human leukemic cells in vitro. J. Biochem. Mol. Biol. 36, 387–389. doi:10.5483/bmbrep.2003.36.4.387

Enayat, S., and Banerjee, S. (2009). Comparative antioxidant activity of extracts from leaves, bark and catkins of Salix aegyptiaca sp. Food Chem. 116, 23–28. doi:10.1016/j.foodchem.2009.01.092

Evans, T. P., Clausen, T. P., Reichardt, P. B., and Chang, S. (1995). Structurally intriguing glucosides from Alaskan littletree willow (Salix arbusculoides). J. Nat. Prod. 58, 1897–1900. doi:10.1021/np50126a015

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.

ACKNOWLEDGMENTS

The authors would like to thank the Egyptian Government for the Ph.D. scholarship of N.T.

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.

Bridle, P., Stott, K. G., and Timberlake, C. F. (1970). Anthocyanins in Salix species: a new anthocyanin in Salix purpurea bark. Phytochemistry 12, 1103–1106. doi:10.1016/0031-9422(73)85023-x
Fayaz, M., and Sivakumaar, P. K. (2014). Phytochemical Analysis and antimicrobial activity of Salix alba against dental biofilm forming bacteria. *Int. J. Pharm. Biol. Arch.* 5, 137–140. doi:10.22377/JPBA.V5.I2.1273

Fernandes, C. C., de Carvalho Cursino, L. M., Novaes, J. d. A. P., Demetrio, C. A., Júnior, O. L. P., Nunez, C. V., et al. (2009). Salicylates isolated from leaves and stems of *Salix martiana* Leyb. (Salicaceae). *Quim. Nova.* 32, 983–986. doi:10.1590/S0100-40422009000400029

Freischmidt, A., Jürgenliemk, G., Kraus, B., Okpanyi, S., Müller, J., Kelber, O., et al. (2010). Phenolic compounds in the ethyl acetate fraction of a standardized willow bark extract. *Planta Med.* 76, 281. doi:10.1055/s-0030-1265481

Gawlik-Dziki, K., Kraus, B., Okpanyi, S., Müller, J., Kelber, O., et al. (2010). Phenolic compounds in the ethyl acetate fraction of a standardized willow bark extract. *Planta Med.* 76, 281. doi:10.1055/s-0030-1265481

Fernandes, C. C., de Carvalho Cursino, L. M., Novaes, J. d. A. P., Demetrio, C. A., Júnior, O. L. P., Nunez, C. V., et al. (2009). Salicylates isolated from leaves and stems of *Salix martiana* Leyb. (Salicaceae). *Quim. Nova.* 32, 983–986. doi:10.1590/S0100-40422009000400029

Freyischmidt, A., Jürgenliemk, G., Kraus, B., Okpanyi, S., Müller, J., Kelber, O., et al. (2010). Phenolic compounds in the ethyl acetate fraction of a standardized willow bark extract. *Planta Med.* 76, 281. doi:10.1055/s-0030-1265481

Gawlik-Dziki, K., Kraus, B., Okpanyi, S., Müller, J., Kelber, O., et al. (2010). Phenolic compounds in the ethyl acetate fraction of a standardized willow bark extract. *Planta Med.* 76, 281. doi:10.1055/s-0030-1265481

Gawlik-Dziki, K., Kraus, B., Okpanyi, S., Müller, J., Kelber, O., et al. (2010). Phenolic compounds in the ethyl acetate fraction of a standardized willow bark extract. *Planta Med.* 76, 281. doi:10.1055/s-0030-1265481

Gawlik-Dziki, K., Kraus, B., Okpanyi, S., Müller, J., Kelber, O., et al. (2010). Phenolic compounds in the ethyl acetate fraction of a standardized willow bark extract. *Planta Med.* 76, 281. doi:10.1055/s-0030-1265481

Fayaz, M., and Sivakumaar, P. K. (2014). Phytochemical Analysis and antimicrobial activity of Salix alba against dental biofilm forming bacteria. *Int. J. Pharm. Biol. Arch.* 5, 137–140. doi:10.22377/JPBA.V5.I2.1273

Fernandes, C. C., de Carvalho Cursino, L. M., Novaes, J. d. A. P., Demetrio, C. A., Júnior, O. L. P., Nunez, C. V., et al. (2009). Salicylates isolated from leaves and stems of *Salix martiana* Leyb. (Salicaceae). *Quim. Nova.* 32, 983–986. doi:10.1590/S0100-40422009000400029
Masika, P., Sultana, N., Afolayan, A., and Houghton, P. (2005). Isolation of two antibacterial compounds from the bark of Salix capensis. South Afr. J. Bot. 71, 441–443. doi:10.1016/s0254-6299(05)30117-4

Mizuno, M., Kato, M., Hosoi, N., Inuma, M., Tanaka, T., Kimura, A., et al. (1990). Phenolic compounds from Salix sachalinensis. Heterocycles 31, 1409–1412. doi:10.3987/com-90-5425

Mizuno, M., Kato, M., Inuma, M., Tanaka, T., Kimura, A., Ohashi, H., et al. (1987). Acylated luteolin glucosides from Salix gligiana. Phytochemistry 26, 2418–2420. doi:10.1016/0031-9422(80)84739-1

Nasudari, A. A., Kompantsev, V. A., Oganesyan, E. T., and Shinkarenko, A. L. (2015). Antimicrobial effect of aqueous extracts of leaves and branches of willow (Salix triandra × Salix capensis). J. Nat. Prod. 78, 609. doi:10.1021/acs.jnatprod.4b00253

Popova, T. P., and Kaleva, M. D. (2015). Antimicrobial effect of lipids from Salix denticulata. J. Nat. Prod. 78, 609. doi:10.1021/acs.jnatprod.4b00253

Prabhjot Kekuda, T., Vinayaka, K., and Raghavendra, H. (2017). Ethnobotanical uses, phytochemistry and biological activities of Salix tetrasperma. Int. J. Curr. Microbiol. Appl. Sci. 6, 146–152.

Rubió, L., Motilva, M.-J., and Romero, M.-P. (2013). Recent advances in biologically active compounds in herbs and spices: a review of the most effective antioxidant and anti-inflammatory active principles. Crit. Rev. Food Sci. Nutr. 53, 943–953. doi:10.1080/10408398.2011.574802

Salem, A.-F. Z., Salem, M. Z., Gonzalez-Ronquillo, M., Camacho, L., and Cipriano, M. (2011). Major chemical constituents of Lescuaena leucocephala and Salix babylonica leaf extracts. J. Trop. Agric. 49, 95–98.

Salem, A. Z., Elghandour, M. M., Kholif, A. E., Lopez, S., Pliego, A. B., Cipriano-Salazar, M., et al. (2017). Tree leaves of Salix babylonica extract as a natural anthelmintic for small-ruminant farms in a semiarid region in Mexico. Agrofor. Syst. 91, 111–122. doi:10.1007/s10457-016-9999-z

Salem, M. A., Hamdan, D. L., Mostafa, I., Adel, R., Elissawy, A., and El-Shazly, A. M. (2020). “Natural products, the new intervention regime of metabolic disorders,” in Natural products in clinical trials, atta-ur-rahman, shazia anjum and hesham R. El-seedi. Singapore: Bentham Book Imprint, Chapter 2, Vol. 2, 32–122.

Sati, S., Singh, H., Badoni, P., and Sati, M. (2013). Screening of fungicidal activity of salix and triumfetta species of garhwal himalaya. AIPCT 1, 486–489.

Semwal, S., Rawat, U., and Sharma, R. K. (2011). Isolation and characterization of a new flavone diglucoside from Salix denticulata. Chem. Nat. Compd. 47, 366. doi:10.1007/s10507-010-9935-z

Shah, Z. A., Hameed, A., Ahmed, A., Simjee, S. U., Jabeen, A., Ullah, A., et al. (2016). Cytotoxic and anti-inflammatory salicin glycosides from leaves of Salix acmophylla. Phytochem. Lett. 17, 107–113. doi:10.1016/j.phytol.2016.07.013

Shao, Y., Lahloud, M., Meier, B., and Sticher, O. (1989). Isolation of phenolic compounds from the bark of Salix pentandra. Planta Med. 55, 617–618. doi:10.1055/s-2006-962172

Siblyou, V. L., and Bardonker, V. G. (1985). Flavonoids of Salix acutifolia. Chem. Nat. Compd. 21, 534. doi:10.1007/bf00757916

Shen, T., Tian, Y.-Q., Liu, W.-X., and Zheng, S.-Z. (2008). Acyclic diterpene-lactones and flavonoid from Salix chelollaphila Omitted. J. Chin. Chem. Soc. 55, 401–405. doi:10.1002/jccs.200800059

Singh, H., Raturi, R., and Badoni, P. (2017). Isolation of secondary metabolites from the roots of salix babylonica. Mater. Sci. Eng. C. 72, 201. doi:10.1016/j.msec.2016.12.013

Sobeh, M., Mahmoud, M. F., Rezq, S., Alsehemy, E. A., Sabry, O. M., Mostafa, I., et al. (2019). Salix tetrasperma roxb. Extract alleviates neuropathic pain in rats via modulation of the NF-κB/TNF-α/NOX/iNOS pathways. Antioxidants 8, 482. doi:10.3390/antiox8100482

Sonbolli, A., Mozarrad, M., Ebrahimi, S. N., and Enayat, S. (2010). Free radical scavenging activity and total phenolic content of methanolic extracts from male inforselescence of Salix aegyptiaca grown in Iran. Iran. J. Pharm. Res. (IJPR) 9, 293–296.

Sulaiman, G. M., Hussien, N. N., Marzooq, T. R., and Awad, H. A. (2013). Phenolic content, antioxidant, antimicrobial and cytotoxic activities of ethanolic extract of Salix alba. Am. J. Biochem. Biotechnol. 9, 41–46. doi:10.3844/ajbbsp.2013.41.46

Sultana, S., and Saleem, M. (2004). Salix caprea inhibits skin carcinogenesis in murine skin: inhibition of oxidative stress, ornithine decarboxylase activity and DNA synthesis. J. Ethnopharmacol. 91, 267–276. doi:10.1016/j.jep.2003.12.028

Tavakoli, F., Rahmani, F., and Heidari, R. (2016). Radical scavenging activity and total phenolic content of methanolic extracts from male inflorescences of Salix aegyptiaca grown in Iran. J. Ethnopharmacol. 195, 201–206.

Tawfeek, N., Sobeh, M., Hamdan, D. I., Farrag, N., Roxo, M., El-Shazly, A. M., et al. (2019). Phenolic compounds from Populus alba L. and Salix sub serrata Wild. (Salicaceae) counteract oxidative stress in Cae morhabditis elegans. Molecules 24, 1999. doi:10.3390/molecules24101999

Thaideo, M., Azevedo, A. A., and Meira, R. M. S. A. (2014). Foliar anatomy of neotropical Salicaceae: potentially useful characters for taxonomy. Plant Systemat. Evol. 300, 2073–2089. doi:10.1007/s00665-014-1037-5

Tuberoso, C. I., Jerković, I., Bifulco, E., and Marijanović, Z. (2011). Biodiversity of Salix subserrata triumfetta. J. Ethnopharmacol. 134, 596–608. doi:10.1016/j.jep.2011.06.010

Tawfeek, N., Sobeh, M., Hamdan, D. I., Farrag, N., Roxo, M., El-Shazly, A. M., et al. (2019). Phenolic compounds from Populus alba L. and Salix sub serrata Wild. (Salicaceae) counteract oxidative stress in Caenorhabditis elegans. Molecules 24, 1999. doi:10.3390/molecules24101999

Vinokurov, I. I. (1979). Flavonoid glycosides of Salix purpurea. Chem. Nat. Compd. 15, 3180–3181. doi:10.1007/bf00874192

Van Wyk, B.-E., and Wink, M. (2018). Natural products, the new intervention regime of metabolic disorders, anti-inflammatory and PAF-induced exocytosis. J. Ethnopharmacol. 206, 61–76. doi:10.1016/j.jep.2017.03.049

Vorupajaksha, J. H., Nadendla, R. R., Kumar, M. S., and Kayva, S. (2016). Effect of Salix tetrasperma Roxburgh leaf extracts on central nervous system activities. Res. J. Pharmacuet. Biol. Chem. Sci. 7, 2060–2064.
Wahid, A., Hamed, A. N., Eltahir, H. M., and Abouzied, M. M. (2016). Hepatoprotective activity of ethanolic extract of Salix subserrata against CCl4-induced chronic hepatotoxicity in rats. *BMC Compl. Alternative Med.* 16, 263. doi:10.1186/s12906-016-1238-2

Wiesneth, S. C. (2019). *Phytochemische Untersuchung des phenolischen Inhaltsstoffspektrums in Salix Spezies unter besonderer Berücksichtigung der Flavan-3-ole*. Ph.D. dissertation. Germany: Universität Regensburg.

Wu, Y., Dobermann, D., Beale, M. H., and Ward, J. L. (2016). Acutifoliside, a novel benzoic acid glycoside from *Salix acutifolia*. *Nat. Prod. Res.* 30, 1731–1739. doi:10.1080/14786419.2015.1137571

Zabihi, N. A., Mahmoudabady, M., Soukhtanloo, M., Hayatdavoudi, P., Beheshti, F., and Niazmand, S. (2018). *Salix alba* attenuated oxidative stress in the heart and kidney of hypercholesterolemic rabbits. *Avicenna J. Phytomed.* 8, 63.

Zaiter, A., Becker, L., Petit, J., Zimmer, D., Karam, M.-C., Baudelaire, E., et al. (2016). Antioxidant and antiacetylcholinesterase activities of different granulometric classes of *Salix alba* (L.) bark powders. *Powder Technol.* 301, 649–656. doi:10.1016/j.powtec.2016.07.014

Zapesochnaya, G. G., Kurkin, V. A., Braslavskii, V. B., and Filatova, N. V. (2002). Phenolic compounds of *Salix acutifolia* bark. *Chem. Nat. Compd.* 38, 314–318. doi:10.1023/a:1021661621628

Zarger, M. S. S., Khatoon, F., and Akhtar, N. (2014). Phytochemical investigation and growth inhibiting effects of *Salix alba* leaves against some pathogenic fungal isolates. *World J. Pharm. Pharmacol.* 3, 1320–1330.

Zeid, A., Hifnawy, M., Saleh, M., Sleem, A., and Mohamed, R. (2006). Phenolics, volatiles and biological activities of *Salix babylonica* L. leaves and stem bark. *Planta Med.* 72, 335. doi:10.1055/s-2006-950135

Zengion, A. H., and Yarnell, E. (2011). "Herbal and nutritional supplements for painful conditions," in *Pain procedures in clinical practice*. Editors T. A. Lennard, S. A. Walkowski, K. A. Singla, and D. Vivian (Philadelphia, PA: Elsevier Saunders), 3, 187–204.

Zhao, L., Liu, L., and Li, J. (2014). Qualitative and quantitative analysis of five bioactive flavonoids in *Salix bordensis* Turcz. by HPLC-DAD and HPLC-ESI-MS. *Am. J. Anal. Chem.* 5, 851. doi:10.4236/ajac.2014.513094

Zhen-Fu, F. (1987). On the distribution and origin of Salix in the world. *J. Systemat. Evol.* 25, 307–313

**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.

Copyright © 2021 Tawfeek, Mahmoud, Hamdan, Sobeh, Farrag, Wink and El-Shazly. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.
GLOSSARY

ABTS 2,2′-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid)
AIDs Acquired immunodeficiency syndrome
Apif Apiofuranosyl
Araf Arabinofuranosyl
Arap Arabinopyranosyl
CCl4 Carbon tetrachloride
C/EBPα CCAAT/enhancer binding protein α
DPPH 2,2-Diphenyl, one- Picryl Hydrazyl
EACC Ehrlich ascites carcinoma cells
EtOAc Ethyl acetate
FRAP Ferric reducing antioxidant power
Glac Galactosyl
Glc Glucosyl
Gluc Glucuronosyl
Hex Hexosyl
HFD High-fat diet
HIV Human immunodeficiency virus
IC50 Half maximal inhibitory concentration
MeOH Methanol
MIC Minimal inhibitory concentration
NF-κB Nuclear factor kappa-B
ORAC Oxygen radical absorbance capacity
Pent Pentosyl
Ph Phenyl
Rh Rhamanosyl
Rut Rutinosyl
SREBP1c Sterol regulatory element binding protein 1
TAC Total antioxidant capacity
TFC Total flavonoid content
TLC Thin layer chromatography
TNF-α: Tumor necrosis factor-alpha
TPC Total phenolic content
XTT 2,3-bis-(2-methoxy-4-nitro-5-sulfophenyl)-2H- tetrazolium-5-carboxanilide
Xylp Xylopyranosyl.