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REVIEW



The genus *Schinus* (Anacardiaceae): a review on phytochemicals and biological aspects

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ABSTRACT

The genus *Schinus* belongs to family ‘Anacardiaceae’ and includes about 29 species originating from South America, distributed to Peru, Chile, Argentina, Brazil and Paraguay and cultivated in Egypt. Traditionally, *Schinus* plants are used to alleviate several and diverse diseases including rheumatism, hypertension, ulcers, gastric distress, menstrual disorders, gonorrhea, bronchitis, gingivitis, conjunctivitis, dysentery, wounds, urinary tract, and eye infections. Several phytochemical studies on the *Schinus* plants revealed presence of diverse bioactive compounds such as flavonoids, bioflavonoids, phenolic acids, tannins, catechins, terpenoids and essential oils. Besides, some *Schinus* species and their isolated active compounds showed important biological activities such as antibacterial, antifungal, insecticidal, antiparasitic, analgesic, cytotoxic, antitumor, antioxidant, antihypertensive, anti-inflammatory, antimycobacterial, anti-Parkinson, anti-allergic, antiviral, wound healing, chemoprotective, anthelmintic and hepatoprotective. This review attempts to summarize the phytochemical profile and biological activities of *Schinus* species that could guide researchers to undertake further investigation.

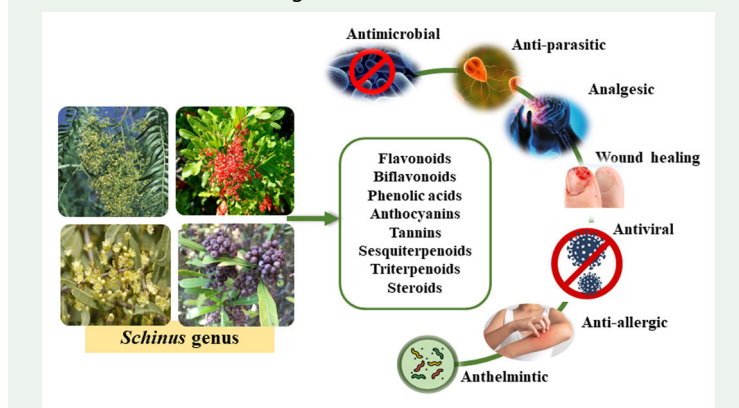
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1. Introduction

The medicinal plants stand as important place with unique significance in many disciplines of the human life (Mohammadhosseini et al. 2021a). Many literature reports of herbal extracts displayed characterization of treasured natural compounds like terpenoids, flavonoids, anthraquinones, alkaloids, coumarins, phenylpropanoids, iridoids, glycosides and essential oils (Mohammadhosseini et al. 2021b). Moreover, the medicinal plants have been taken a vital role in the ethnobotanical aspects and traditional folk medicine due to diverse biological properties worldwide (Nahar et al. 2021). The genus *Schinus* L. (Anacardiaceae) comprises approximately 29 species distributed from Mexico to Argentina, extending from Central to South America, through Mexico, Colombia, Ecuador, Peru, Bolivia, Chile, Argentina, Paraguay, and Uruguay (Barbosa et al. 2007). The *Schinus* plants are dioecious and female trees that produce large crops of small bright berries arranged in bunches on pendulous stems (El-Nashar et al. 2019). Many plants belonging to this genus are known as traditional medicines for the treatment of several and diverse pathologies including rheumatism, bronchial infections, high blood pressure, ulcers, stomach upset, menstrual disorders, gonorrhea, bronchitis, conjunctivitis, dysentery, wounds, urinary affections, gingivitis and eye infections (Murray et al. 2012; Elkhawas et al. 2020). The fruits of *Schinus* plants are also used in syrups, vinegar, and beverages in Peru as well as in Chilean wines (Ayoub et al. 2010; Affonso et al. 2012). In some countries, the dried and ground fruits have been used in the perfume industry (El-Massry et al. 2009; Abd El-Ghffar et al. 2021).

Phytochemically, these plants are rich in many potentially active compounds from all classes of secondary metabolites, including flavonoids, biflavonoids, tannins, catechins and sesquiterpenes, triterpenes and steroids (Farak 2008; Todirascu-Ciornea et al. 2019). This review aimed to aim collect and summarized all updated information about the isolated phytochemicals and biological activities of several species from genus *Schinus*.

2. Traditional uses

Schinus species were reported for different traditional uses as illustrated in Table S1.

3. Isolated phytochemicals

3.1. Flavonoids

Flavonoids are the most abundant category of phytochemicals found in the *Schinus* plants as shown in Figure 1. Among these flavonoids, quercetin **1** was isolated from the leaves of *S. polygamus* leaves (Erazo et al. 2006; El-Sayed 2016), *S. lentiscifolius* (Gehrke et al. 2013) and *S. molle* (Ibrahim and Haggag 2013; Garzoli et al. 2019). Also, quercetin-3-O- β -D-glucoside **2** was identified in the leaves of *S. longifolius* and *S. molle* (Marzouk et al. 2006), as well as the bark of *S. molle* (Saleh et al. 1969). The aqueous methanolic extract of *S. molle* yielded four flavonoid glycosides namely, quercetin-3-O- β -D-glucuronoside **3**, quercetin-3-O- β -D-galactoside **4**, quercetin-3-O- β -D-galactouronoside **5**, and rhamnetin-3-O- β -D-⁴C₁-galactoside **6** (Marzouk et al. 2006; Ibrahim and

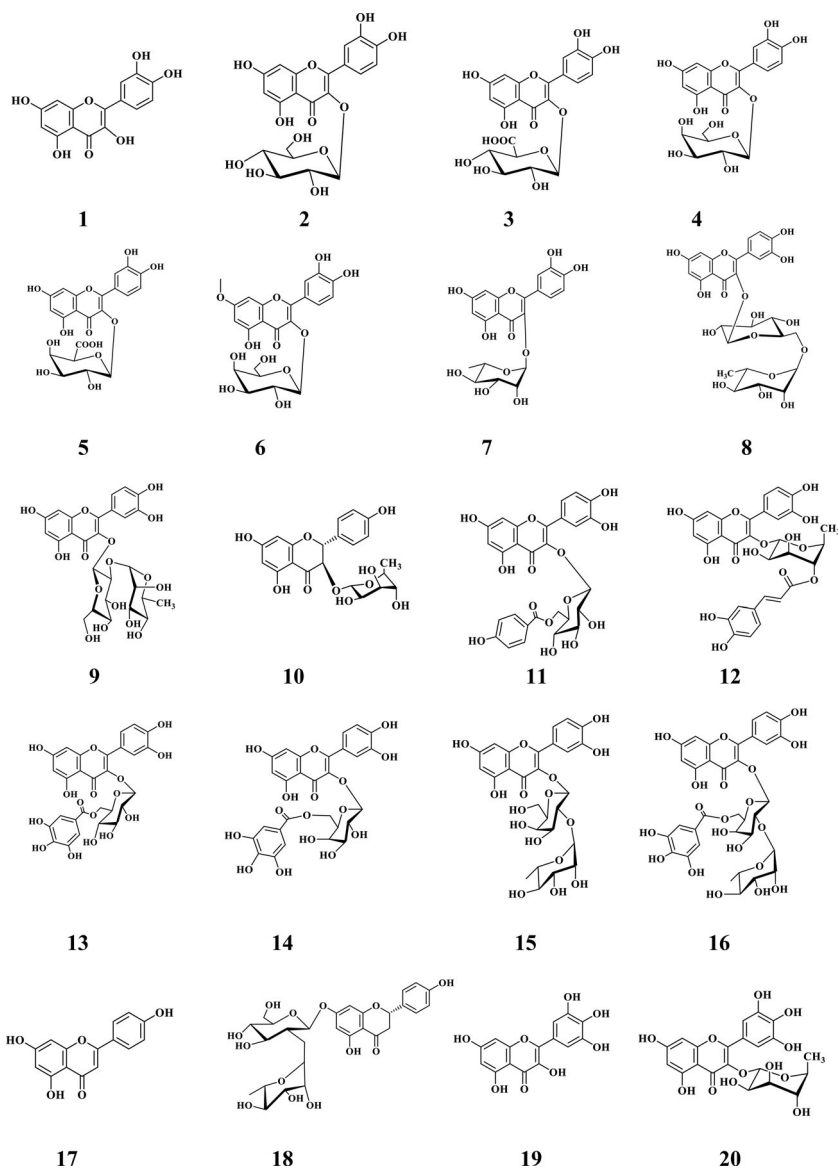


Figure 1. Structures of flavonoids isolated from *Schinus* plants.

Haggag [2013](#)). Another flavonoid namely, quercetin-3-*O*- α -L-rhamnoside **7** was predominant in the *Schinus* plants including *S. terebinthifolius* (Ceruks et al. [2007](#)), *S. mole* (Ibrahim and Haggag [2013](#)), *S. lentiscifolius* (Gehrke et al. [2013](#)), and *S. polygamus* (El-Sayed [2016](#)). Different reports described isolation of quercetin-3-*O*-rutinoside **8** from the leaves of *S. molle*, *S. longifolius* and *S. lentiscifolius* (Graziano et al. [1970](#); Rahman et al. [1974](#); Machado et al. [2008](#)). Further, quercetin 3-*O*- β -D-neohesperidoside **9** was isolated from *S. molle* leaves (Marzouk et al. [2006](#)). Engeletin **10** was identified in the fruits of *S. molle* (Ono et al. [2008](#)). Four acylated quercetin glycosides namely, isoquercitrin 6''-*O*-*p*-hydroxybenzoate **11**, quercitrin 2''-*O*-cafeate **12**, isoquercitrin 6''-*O*-gallate

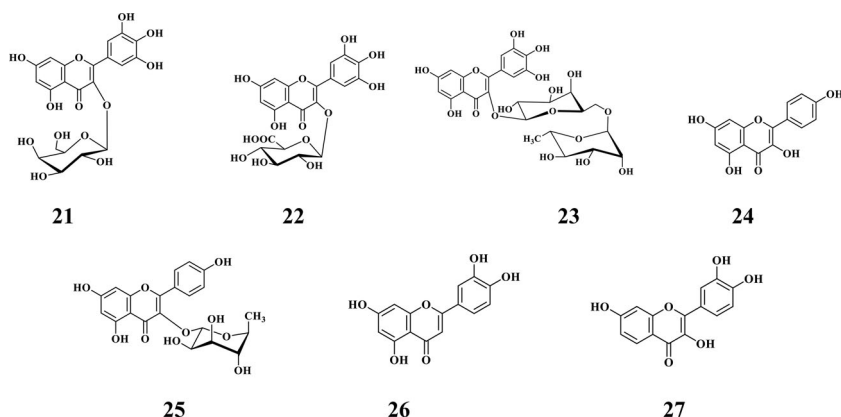


Figure 1. Continued.

13, hyperin 6''-O-gallate **14** were found in the aerial parts of *S. molle* (Marzouk et al. 2006; Ibrahim and Haggag 2013). Two hyperin glycoside derivatives, 2''-O-α-L-rhamnopyranosyl-hyperin **15** and 2''-O-α-L rhamnopyranosyl-hyperin 6''-O-gallate **16** were reported in the leaf extract of *S. molle* (Marzouk et al. 2006). In a study carried out by Ceruks et al. (2007), it described isolation of apigenin **17**, naringine **18**, myricetin **19** from *S. terebinthifolius* leaves. Another study revealed isolation of four myricetin glycosides namely, myricetin-3-O-α-L-rhamnoside **20**, myricetin –3-O-β-D-galactoside **21**, myricetin-3-O-β-D-glucuronoside **22**, myricetin-3-O-α-L-rhamnopyranosyl (1'''-6'') β-D-galactoside **23** from *S. terebinthifolius* leaves (Farg 2008). Further, the leaves of *S. polygamus* and *S. terebinthifolius* were reported to contain kaempferol **24**, kaempferol-3-O-α-L-rhamnoside **25** (Cerus et al. 2007; El-Sayed 2016). Luteolin **26** was isolated from *S. terebinthifolius* leaves (Carvalho et al. 2013; Fedel-Miyasato et al. 2014). Besides, fisetin **27** was isolated from the bark of *S. molle* (Saleh et al. 1969).

3.2. Biflavonoids

Biflavonoids are characteristic class of polyphenolics in *Schinus* plants (Figure S1). Among this class, agathisflavone **28** is the major one isolated from several *Schinus* species such as *S. molle* fruits (Yueqin et al. 2003), *S. terebinthifolius* fruits (Kassem et al. 2004; Feureisen et al. 2014), and *S. polygamus* leaves (Dumitru et al. 2019). Further, chamaejasmin **29** and tetrahydroamentoflavone **30** were isolated from *S. molle* fruits (Yueqin et al. 2003). Besides, four biflavonoids; robustaflavone **31**, tetrahydrorobustaflavone **32**, amentoflavone **33**, and 2,3-dihydro amentoflavone **34** were isolated from *S. terebinthifolius* fruits (Skopp and Schwenker 1986; Kassem et al. 2004; Feureisen et al. 2014). Also, El-Nashar et al. (2020b) has been reported a new biflavonoid skeleton namely, luteolin-(6→8'')-apigenin **35** from the methanol extract of *S. polygamus* leaves.

3.3. Phenolic acids and their derivatives

Phenolic acids and their derivatives are presented in Figure S2. Gallic acid **36**, and its derivatives; methyl gallate **37** and ethyl gallate **38** were the predominant compounds

isolated from the leaves of *S. terebinthifolius* (Amal et al. 2007; Ceruks et al. 2007; Rosas et al. 2015), *S. molle* (Marzouk et al. 2006), *S. lentiscifolius* (Graziano et al. 1970; Gehrke et al. 2013) and *S. polygamus* (El-Sayed 2016). Also, syringic acid **39** and 5-O-caffeoylquinic acid **40** were found in the leaves of *S. mole* and *S. terebinthifolius* (Marzouk et al. 2006; El-Massry et al. 2009). Further, ellagic acid **41**, coumaric acid **42**, caffeic acid **43**, 5-O-coumaroylquinic acid **44**, shikimic acid **45**, protocatechuic acid **46**, chlorogenic methyl ester **47**, cinnamic acid **48** and amino cinnamic acid **49** were purified from the leaves of *S. terebinthifolius*, *S. polygamus* and *S. molle* (Ceruks et al. 2007; El-Massry et al. 2009; Fedel-Miyasato et al. 2014).

Amal et al. (2007) has characterized two phenolic acid derivatives namely, *p*-aminophenyl acetic acid **50** and 2-phenylacetamide **51** from the leaves of *S. terebinthifolius*. Besides, three biphenyl derivatives, 4'-ethyl-4-methyl-2,3',5',6-tetrahydroxy [1,1'-biphenyl]-4,4'-dicarboxylate **52**, 3-ethyl-3'-methyl-4,4',5,5',6,6'-hexahydroxy-[1,1'-biphenyl]-3,3'-dicarboxylate **53** and 4'-ethyl-4-methyl-2,2',6,6'-tetrahydroxy-[1,1'-biphenyl]-4,4'-dicarboxylate **54** were identified in the fruit extract of *S. terebinthifolius* (Kassem et al. 2004; Johann et al. 2010).

3.4. Anthocyanins

Four compounds of anthocyanins namely, cyanidin-3-O- β -D-galactoside (**55**), peonidin-3-O- β -D-galactoside **56**, malvidin-3-O- β -D-galactoside **57**, cyanidin-3-O-rutinoside **58** and malvidin-3-O-rutinoside **59** were identified in *S. longifolius* leaves, *S. molle* leaves and *S. terebinthifolius* fruits (Rahman et al. 1974; Feuereisen et al. 2014). Another three anthocyanin analogues were characterized as pelargonidin-3-O- β -D-galactoside **60**, 7-O-methylcyanidin-3-O- β -D-galactoside **61** and 7-O-methyl pelargonidin-3-O- β -D-galactoside **62**. The chemical structures of isolated anthocyanins are presented in Figure S3.

3.5. Tannins and catechins

The leaves of *S. terebinthifolius* were reported to be rich in galloylated compounds (hydrosable tannins) such as 1,6-digalloyl-O- β -D-glucoside **63** and 1,2,3,4,6-penta-O-galloyl- β -D-glucoside **64** as shown in Figure S4 (Carvalho et al. 2013). On another side, (+)-catechin **65** was found in the leaf extract of *S. molle* and *S. terebinthifolius* (Marzouk et al. 2006; Farag 2008).

3.6. Terpenoids

3.6.1. Sesquiterpenoids

Sesquiterpenoids represents a major class of compounds in *Schinus* plants (Figure S5). A group of researchers isolated six sesquiterpenoids of guaiene skeleton from the methanol extract of *S. molle* collected from Peru (Ono et al. 2008). These compounds were identified as chrysothol **66**, teucladiol **67**, 4b,6b-dihydroxy-1a,5b (H)-guai-9-ene **68**, 4 β ,6 β -dihydroxy-10a-methoxy-1 α ,5 β ,7 α (H)-guaiane **69**, teuclatriol **70** and 10-Epiteuclatriol **71**. Besides, six cadinol derivatives namely, oplodiol **72**, oplopanone **73**, isocalamediol **74**, α -cadinol methyl ether **75**, 1 β ,6 α -dihydroxy-7-epieudesm-3-ene **76** and 1 β ,6 β -dihydroxy-7-epieudesm-3-ene **77** were identified in the same extract.

Further, β -spathulene **78** and pathulenol **79** were isolated from *S. molle* fruits in Mexico. Two novel *spiro*-sesquiterpenes, 9-*spiro*-cyclopropa-4,4,8-trimethyl-2-methylen-bicyclo-[4.3.0]-non-1(6)-ene (terebanene, **80**) and 9-*spiro*-cyclopropa-2,4,4,8-tetramethyl-bicyclo-[4.3.0]-nona-1,5-diene (teredenene, **81**) were characterized in the fruit extract of *S. terebinthifolius* (Richter et al. 2010). In 2017, another *spiro*-sesquiterpene was characterized as (6*R**,8*R**)-9-*spiro*-cyclopropa-2,4,4,8-tetramethyl bicyclo[4. 3.0] non-1-ene (terebinthene, **82**) in the resin extract of *S. molle* bark (Malca-García et al. 2017).

3.6.2. Triterpenoids

As illustrated in Figure S6, four oleanane-type triterpenoids, α -amyrin **83**, β -amyrin **84**, α -amyrone **85** and baurenene **86** were isolated from different parts of *S. terebinthifolius* (de Paiva Campello and Marsaioli 1975; Lloyd et al. 1977). Three compounds of the ursane type identified as terebinthifolic acid **87**, moronic acid **88** and ursolic acid **89** were isolated from *S. lentiscifolius* aerial parts (Gehrke et al. 2013) and *S. terebinthifolius* fruits (Lloyd et al. 1977).

El-Sayed (2016) carried out phytochemical studies on the methanolic extract of *S. polygamus* leaves and isolated two lupane-type triterpenes, lupeol **90** and 3-*O*-acetyl-lupeol **91**. Another two lupane-type triterpenes, simiarenol **92** and simiarenone **93** were identified from *S. terebinthifolius* fruits (de Paiva Campello and Marsaioli 1975; Lloyd et al. 1977).

3.7. Steroids

Different reports described isolation of steroids from *Schinus* plants as shown in Figure S7. Among these compounds, campesterol **94** and β -sitosterol **95** were purified from *S. longifolius*, *S. polygamus*, *S. molle* and *S. terebinthifolius* (Erazo et al. 2006; El-Sayed 2016). Also, masticadienonic acid (**94**) and its derivatives, 3 α -hydroxymasticadienonic acid **96**, isomasticadienonic acid **97**, isomasticadienonic acid **98**, 3-*epi*-isomasticadienonic acid **99**, 3-*epi*-isomasticadienonic acid **100**, (13 α , 14 β ,17 α , 20*S*,24*Z*)-3 α -hydroxylanosta-8,24-dien-26-oic acid **101**, (13 α , 14 β ,17 α , 20*R*, 24*Z*)-3 α -hydroxy-21-oxo-lanosta-8,24-dien-26-oic acid **102** and (13 α , 14 β , 17 α , 20*S*, 24*Z*)-3 α -Hydroxy-21-oxolanosta-8,24-dien-26-oic acid **103** were found in the leaves and fruits *S. molle* (Ono et al. 2008; Malca-García et al. 2017).

Five new steroids of tirucalladiene class namely, 3-oxo-8, 24-tirucalladien-21-oic acid **104**, 3 β -hydroxy-8,24 (*Z*)-tirucalladien-21-oic acid **105**, 3 α -hydroxy-8, 24 (*Z*)-tirucalladien-26-oic acid **106**, 24-(*Z*)-isomasticadienonic acid **107**, 7,11-dioxo-3 α -hydroxy-8,24-(*Z*)-tirucalladien-26-oic acid **108** and 3-oxo-5 α -lanosta-8,24-diene-21-oic acid (Pinicolic acid, **109**) were reported in *S. molle* fruits (Ono et al. 2008).

3.8. Essential oils

The *Schinus* plants are rich source of essential oils. Scheme S1 illustrates briefly the major identified components of essential oils isolated from different *Schinus* Species

(Maffei and Chialva 1990; Murray et al. 2005; Urzua et al. 2011; Martins et al. 2014; Rey-Valeirón et al. 2017; El-Nashar et al. 2020a).

3.9. *Miscellaneous compounds*

Different phytochemical studies of *S. molle* leaves and fruits revealed presence of lignoceric acid **110**, preisocalamenediol **111** and piperine **112** as illustrated in Figure S8 (Kramer 1957; Dominguez et al. 1971; Delvalle and Schwenker 1987).

4. Biological studies

Schinus species have been used for centuries as folk remedy because of their diverse biological activities. The genus is rich source of bioactive compounds as abovementioned, which are implicated in the reported biological activities of the genus *Schinus*. The crude extracts as well as isolated pure compounds possess a number of promising biological activities. These activities of *Schinus* plants are briefly described here.

4.1. *Antimicrobial activities*

The chloroform extract of the bark resin obtained *S. molle* showed inhibitory activity against *Staphylococcus aureus* ATCC 25923 and *Bacillus subtilis* ATCC 6633 with MIC values of 8.0 and 0.125 mg/mL, respectively (Malca-García et al. 2017). Among the isolated components, terebinthene **82** and pinicolic acid **109** displayed antibacterial activity against all tested bacterial strains at different concentrations. Also, the *n*-hexane and petroleum ether extracts of *S. molle* fruits grown in Syria were evaluated for antifungal activity (Ibrahim and Al-Naser 2014). These extracts suppressed the growth of *Botrytis cinerea* completely at dose of 1000 ppm. The essential oil (EO) isolated from *S. molle* fruits in Turkey displayed weak antimicrobial activities against *Bacillus subtilis* ATCC 6051, *Escherichia coli* ATCC 11775, *Staphylococcus aureus* ATCC 12600, *Pseudomonas aeruginosa* ATCC 10145, *Salmonella typhimurium* ATCC 25241, *Enterococcus faecalis* ATCC 29212, *Candida albicans* ATCC 10231 and *Saccharomyces cerevisiae* ATCC 2601, compared to ampicillin and ofloxacin (Eryigit et al. 2017; Mostafa 2018). Furthermore, the same authors reported the antimicrobial activity of EO isolated from *S. molle* leaves and fruits against eight bacterial strains; *Staphylococcus epidermidis* ATCC 12228, *Staphylococcus aureus* ATCC 29213, *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853, *Enterococcus faecalis* LFG 01, *Proteus mirabilis* LFG 04, *Salmonella enteritidis* LFG 05 and *Salmonella Typhimurium* LFG 06 as well as six fungal strains; *Aspergillus niger*, *Aspergillus japonicus*, *Aspergillus oryzae*, *Fusarium oxysporum*, *Rhizopus oryzae* and *Rhizopus stolonifera* (Martins et al. 2014; Cutro et al. 2021). On other hand, The inclusion of EO obtained from *S. molle* in chitosan bionanocomposites exhibited antifungal activity against *Aspergillus parasiticus* spores decreasing their viability by 40-50% (Luque-Alcaraz et al. 2016). Also, the EO and aqueous extract of Egyptian *S. molle* wood branches showed a marked antibacterial activity against *Staphylococcus aureus*, *Micrococcus luteus*, *Bacillus subtilis*, *Bacillus cereus*, *Escherichia coli*, *Sarcina lutea* and *Pseudomonas aeruginosa* (Salem et al. 2016).

The decoction of *S. lentiscifolius* leaves exerted inhibitory activity against different bacterial strains; *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Staphylococcus saprophyticus*, *Streptococcus pyogenes*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Shigella sonnei* with MIC values ranging from 125 to 250 µg/mL (Gehrke et al. 2013). Meanwhile, the *n*-hexane extract displayed a weak antibacterial activity, but it exerted a significant antifungal activity against *Candida albicans*, *Candida tropicalis*, and *Cryptococcus neoformans* with MIC values of 25, 15.5 and 15.5 µg/mL, respectively. It was found that moronic acid **88** was the active antibacterial metabolite with MIC ranging between 1.5 and 3 µg/mL.

The 70% hydroalcoholic extract of *S. terebinthifolius* Raddi bark was screened for inhibitory effect against bacterial strains obtained from the American Type Culture Collection (ATCC) (Nogueira Sá et al. 2014). The extract demonstrated a remarkable inhibitory activity against the bacterial growth of *Staphylococcus aureus* 6538 forming zones of inhibition of 8.0 mm with MIC of 35.3 mg/mL, while the other tested bacterial strains; *Pseudomonas aeruginosa* 8027, *Staphylococcus aureus* 25925 and *Escherichia coli* 10536 showed no response to the extract. One other side, the EO of *S. terebinthifolius* fruits was evaluated for antibacterial activity against wild bacterial strains of hospital origin (*Escherichia coli*, *Pseudomonas* sp., *Klebsiella oxytoca*, *Corynebacterium* sp., *Staphylococcus aureus*, *Enterobacter* sp., *Enterobacter agglomerans*, *Bacillus* sp., *Nocardia* sp. and *Streptococcus* group D) using broth dilution method (Cole et al. 2014). The tested EO was able to inhibit all tested microorganisms with minimum inhibitory concentration ranging from 3.55 to 56.86 µg/mL. da Silva Dannenberg et al. (2016) investigated the bio-preservative activity potential of EOs isolated from green and mature fruits *S. terebinthifolius* (GEO and MEO) against eighteen food bacterial strains and in situ (Minas-type fresh cheese) against *Listeria monocytogenes* during storage (30 days/4 °C). The MEO showed the highest activity against *L. monocytogenes* with MBC of 6.8 mg/mL and reduced the growth level of *L. monocytogenes* by 1.3 log CFU/g in 30 days. These results demonstrated the MEO could be a candidate for partial or total replacement of undesired synthetic preservatives in food industries. Piras et al. (2017) reported the antifungal activity of EO isolated from Tunisian *S. terebinthifolius* leaves and fruits against *Cryptococcus neoformans* and *Candida albicans* with MIC values ranging between 0.32 and 0.64 mg/mL. The antimicrobial activity of ethanolic extract and EOs of *S. terebinthifolius* leaves were reported against *Staphylococcus aureus* ATCC 25923, *Escherichia coli* ATCC8739 and *Candida albicans* ATCC10231 (Uliana et al. 2016). Also, the ethanolic extract of *S. terebinthifolius* fruits and leaves exerted inhibitory activity against *Escherichia coli*, methicillin-resistant *Staphylococcus aureus* (MRSA), *Cryptococcus neoformans* and *Candida albicans* where *E. coli* was the most sensitive microorganism showing with MIC of 78 µg/mL (da Silva et al. 2017). The hydroalcoholic extract of *S. terebinthifolius* showed a significant anti-adherent activity to the bio-films formed by *Streptococcus mutans* UA159 and *Candida albicans* ATCC10231 (Barbieri et al. 2014). In other study carried out by Gomes et al. (2013), lectin was isolated and purified from *S. terebinthifolius* leaves, then evaluated for antimicrobial activity. The lectin showed a potent antimicrobial activity against *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Salmonella enteritidis*, *Staphylococcus aureus* and *Candida albicans*. The lectin acts through the interaction with N-acetyl glucosamine of the fungal and bacterial cell wall, further studies are

recommended for evaluation of toxicity in humans. Regarding antituberculosis effect, Bernardes et al. (2014) reported that the methanolic extract, flavonoid fraction and apigenin **17** isolated from the *S. terebinthifolius* Raddi fruits exhibited a significant concentration-dependent inhibitory effect against *Mycobacterium bovis* BCG. Apigenin **17** was more active than the crude extract and flavonoid fraction, with MIC values of 14.53 ± 1.25 , 279.5 ± 1.14 and 108.5 ± 1.05 $\mu\text{g/ml}$, respectively. The reported antimicrobial activities of *Schinus* plants are summarized in Table S2.

4.2. Insecticidal and repellent activities

The insecticidal activity of *n*-hexane extract and EO of *S. molle* were reported against *Ctenocephalides felis* eggs and adults (Abdel-Sattar et al. 2010; Batista et al. 2016). The *n*-hexane extract showed LD_{50} values of $524.80 \mu\text{g/cm}^2$ while the EO from fruits and leaves showed LD_{50} values of 353.95 and $12.02 \mu\text{g/cm}^2$, respectively. On another hand, Lopez et al. compared the efficiency of insecticidal activity related to the free EO of *S. molle* leaves and its microcapsule formulation against *Haematobia irritans* (López et al. 2014). The authors reported that the microcapsule EO formulation showed a slower time-dependent insecticide effect (32 and 73% of dead flies at 2 and 4 h of exposure time) compared to the free EO (96% of dead flies at 2 h). Girmay et al. (2014) proved the larvicidal and pupicidal activities of aqueous and ethanol extract of *S. molle* (leaves, immature fruits, and mature fruits) against filarial vector, *Culex quinquefasciatus*. Further phytochemical investigation and formulation studies are warranted to develop effective formulation for control of filariasis. Furthermore, the EO obtained from *S. molle* demonstrated acaricidal effect on larvae of *Rhipicephalus microplus* (Rey-Valeirón et al. 2017).

Santos et al. (2013) reported the insecticidal activity of EO isolated from *S. terebinthifolius* leaves against *Hypothenemus hampei*. The isolated EO was diluted in acetone (10-2 to 10-8) and applied. The topical application of two EO dilutions resulted in mortality rates of 97.5%–77.5%, respectively. Also, the EO from *S. terebinthifolius* Raddi fruits showed repellent and insecticidal effects against *Bemisia tabaci* and *Trialeurodes ricini* (Hussein et al. 2017). The tested EO showed greater repellency against *Bemisia tabaci* (37.84%) with LC_{50} value of 19.622 ppm. Further studies are recommended to clarify the mode of action to be used as alternative insecticidal agent for protection of crops from white flies. The larvicidal activity of *S. terebinthifolius* leaves was investigated against *Aedes aegypti* larvae (Procópio et al. 2015). The mode of action is mediated through damage of digestive, enteroendocrine, and regenerative cells in larvae midgut, as well as induction of structural disorganization of the gut and elimination of the gut content affecting survival and development.

4.3. Anti-parasitic activity

The *n*-hexane extract of *S. terebinthifolius* leaves demonstrated a trypanocidal activity against *Trypanosoma cruzi* with IC_{50} values ranging between 15 and $58 \mu\text{g/mL}$ and leishmanicidal activity against amastigotes of *Leishmania infantum* with an IC_{50} values between 28 and $97 \mu\text{g/mL}$ (Morais et al. 2014).

Among ten Mexican medicinal plants, the methanolic extract of *S. molle* showed pronounced trypanocidal activity against epimastigotes of *Trypanosoma cruzi* with growth inhibition ranging between 88% and 100% at concentration of 150 µg/mL (Molina-Garza et al. 2014). Also, the nanoemulsion formulation from EO of *S. molle* was investigated for antiparasitic activity against *Trypanosoma evansi* for different concentrations (0.5%, 1.0% and 2.0%), compared to diminazene aceturate as positive control (Baldissera et al. 2013). The formulated nanoemulsion demonstrated time and concentration-dependent reduction of parasite number. Moreover, Quintanilla-Licea et al. (2014) proved the antiprotozoal activity of the methanolic extract of *S. molle* aerial parts against *Entamoeba histolytica*. The extract (150 µg/mL) exerted 81.79% growth inhibition with IC₅₀ values ranging from 32.45 to 98.75 µg/mL, far less effective than metronidazole (IC₅₀ = 0.205 µg/mL).

4.4. Analgesic activity

The dichloromethane extract of *S. molle* seeds significantly increased the tail flick latency providing better and more long lasting protection against thermal pain (Taylor et al. 2016). The EO isolated from *S. terebinthifolius* fruits (100 mg/kg) and its major components as (*R*)-(+)-limonene and α-phellandrene, demonstrated antihyperalgesic activity. The oral administration of (*R*)-(+)-limonene (10 mg/kg) inhibited the mechanical sensitivity and immobility induced by spared nerve injury (SNI) while only α-phellandrene inhibited cold hyperalgesia in SNI rats. The findings of this study justified the traditional use of *S. terebinthifolius* to combat the pain disease. Further clinical trials are recommended to provide new possibilities for the development of new antihyperalgesic herbal drug (Piccinelli et al. 2015).

4.5. Cytotoxicity and antitumor activities

The EO from *S. molle* leaves growing in Saudi Arabia showed a promising cytotoxic activity against HepG2 cell line with IC₅₀ value of 16.33 ± 0.78 µg/mL (Abdel-Hameed and Bazaid 2017). Also, the EO obtained from different parts of *S. molle* (fruit, leaf, stem and flower) were investigated for cytotoxic activities against breast carcinoma (MCF-7), hepatocellular carcinoma (HepG2) and human colon carcinoma (HCT-116) cell lines (Díaz et al. 2008; Hamdan et al. 2016; Ovidi et al. 2021). Among the tested oils, the fruit oil exhibited the most pronounced inhibitory activity against HCT-116 and HepG2, with IC₅₀ values of 1.15 and 0.95 µg, respectively, while MCF-7 was the most sensitive to flower oil (IC₅₀ = 0.98 µg). The phytochemical investigation of *S. molle* extract revealed characterization of four terpenes identified as terebinthene **82**, isomasticadienonic acid **97**, isomasticadienonic acid **98** and pinicolic acid **109** (Malca-García et al. 2017). Among these components, terebinthene **82** significantly inhibited the growth of HCT-116 cells with IC₅₀ value of 14.23 ± 1.3 µg/mL.

4.6. Antioxidant activity

The EO of Egyptian *S. molle* leaves exhibited a promising 2,2-diphenylpicrylhydrazyl (DPPH) scavenging activity, with IC₅₀ of 172.41 µg/mL (Romeilah et al. 2016). Also, the

EO and aqueous extract of *S. molle* wood branches showed significant antioxidant activities with IC_{50} values of 12.66 ± 2.15 and $13.11 \pm 3.00 \mu\text{g/mL}$, respectively (Salem et al. 2016). According to trolox equivalent antioxidant capacity method, the EO of *S. molle* fruits from turkey displayed weak radical scavenging activities with trolox values of $4.7 \pm 1.2 \text{ mM}$ (Eryigit et al. 2017). Moreover, Martins et al. reported that leaf and fruit EO of *S. molle* enhanced a free radical scavenging effect by 4.8% and 5.5%, respectively, using the DPPH radical method (Martins et al. 2014). Also, leaf and fruit EO (1 mg/mL) significantly inhibited lipid peroxidation by 57% and 19%, respectively, compared to ascorbic acid (1%).

An antioxidant comparative study was assessed for the EO, dichloromethane and ethanolic extracts of the Egyptian *S. terebinthifolius* leaves using DPPH and β -carotene/bleaching assays (El-Massry et al. 2009; Uliana et al. 2016; Iwanaga et al. 2019). The highest antioxidant activity was shown by ethanolic extract, followed by EO and dichloromethane extract.

4.7. Antihypertensive activity

de Lima Glória et al. (2017) identified two phenolic compounds; naringin **18** and gallic acid **36** from the methanol extract of *S. terebinthifolius* fruits and reported their antihypertensive activity. The isolated compounds significantly decreased the systolic, median, and diastolic arterial pressures in Wistar rats after intravenous administration. Moreover, the vasodilator action was mediated through direct action on CNS, with an effect on the peripheral musculature, compared to diazepam as positive control.

4.8. Anti-inflammatory activity

The dichloromethane extract of *S. molle* seeds significantly reduced rat paw edema compared to ibuprofen (Taylor et al. 2016).

The hydro-alcoholic extract of *S. terebinthifolius* leaves exerted a dose-dependent anti-inflammatory activity (Rosas et al. 2015). The effective dose (100 mg/kg) inhibited 70% of neutrophil accumulation, compared to the control group in zymosan-induced-arthritis model. Also, it reduced joint diameter and neutrophil influx for synovial tissues, inhibited synovial interleukin (IL)-6, IL-1 β , keratinocyte-derived chemokine (CXCL1/KC) and tumor necrosis factor (TNF)- α production. In addition, the extract was safe, compared to diclofenac which induced gastric damage and animal death by similar doses. This study proved the therapeutic potential of *S. terebinthifolius* for joint inflammation. Moreover, the methanolic extract of *S. terebinthifolius* leaves showed anti-inflammatory activity similar to that of dexamethasone for edema reduction (Fedel-Miyasato et al. 2014). It hindered the leukocyte migration and diminished plasma extravasation. Also, the extract demonstrated wound-healing and chemopreventive properties like collagenase effects. Likewise, the same extract induced apoptosis and upgraded splenic phagocytosis in animals treated with cyclophosphamide. Further studies are recommended to correlate the medicinal properties of the extract against different type of cancers originating from inflammatory processes, such as melanoma and colon cancer.

4.9. Wound healing activity

A formulation of ointment containing EO of *S. terebinthifolius* leaves was reported to promote the tissue repair process and lesion healing (Estevão et al. 2013). Also, the morphological studies showed a significant increase in the quantification of collagen fibers, compared to the control group. Additional studies are recommended to establish the optimal concentration to be used as alternative medicine for cutaneous wounds and to define the regulatory mechanisms of collagen synthesis and epithelial regeneration.

4.10. Anti-Parkinson activity

The 70% ethanolic extract of *S. terebinthifolius* stem bark showed neuroprotective effects against behavioral and biochemical changes of Parkinson disease induced by rotenone in rats (Sereniki et al. 2016). The rotenone administration (3 mg/kg, s.c) produced hypolocomotion, increment of immobility and muscle incoordination, while the treatment with *S. terebinthifolius* extract showed a dose-dependent improvement in rotenone-induced dysfunctional behavior. The biochemical investigation of the substantia nigra, striatum and cortex revealed that *S. terebinthifolius* significantly decreased lipid peroxidation, which was elevated by rotenone administration.

4.11. Anti-allergic activity

The ethanolic extract of *S. terebinthifolius* bark was reported for antihistaminic activity (Nunes-Neto et al. 2017). The different doses extract (100, 200, and 400 mg/kg) decreased histamine-induced paw edema and in rats by 33.9%, 48.4%, and 54.8%, respectively. Moreover, the extract selectively reduced the guinea pig ileum contractions induced by histamine in concentration-dependent manner, while the contractions induced by carbachol, and potassium chloride did not respond to the extract. In addition, the co-administration of the extract and hydroxyzine potentiated the antihistaminic effects. Therefore, it was proposed that the extract may act directly on the histaminergic receptor or signaling pathway, since the effects induced by verapamil on the muscarinic receptors was not changed by the extract. Accordingly, the extract could be utilized for allergic conditions triggered by histamine.

4.12. Antiviral activity

The crude hydroethanolic extract (CHE) of *S. terebinthifolius* stem bark elicited anti-herpes simplex virus type-1(HSV-1) activity using sulforhodamine B colorimetric method (Nocchi et al. 2016). The authors suggested that the CHE interfered with the viral entry process through masking viral receptors that are crucial for adsorption or entry into host cells. Additionally, Nocchi et al. (2017) conducted *in vivo* antiviral studies reporting that the CHE showed no genotoxic effects and demonstrated protective activity against lesions caused by HSV-1. Further experiments are recommended to elucidate the mechanism of action, as well as preclinical and clinical trials to guarantee its safety and efficacy.

Another study on the EO of Egyptian *S. molle* leaves showed inhibitory effect against with HSV-1 with an IC_{50} value of 48.06 μ g/mL and selectivity index (SI) of 9.91 using RC-37 cells as a host cells (Romeilah et al. 2016). Additionally, the authors reported that the anti-HSV activity proceeded via direct interaction with free virus particles.

4.13. Chemoprotective activity

The methanolic extract of *S. terebinthifolius* Raddi leaves exhibited a chemoprotective activity against doxorubicin-induced cardiotoxicity in mouse hearts (da Rocha et al. 2018). Also, the extract hindered the oxidative hemolysis and lipid peroxidation in erythrocytes incubated with doxorubicin. Moreover, the extract augmented the activity of superoxide dismutase and glutathione peroxidase in the erythrocytes. However, the extract did not influence the cytotoxic action of doxorubicin in K562 human erythroleukemia cells. The clinical trials are required to ascertain use of the extract as an adjuvant treatment with chemotherapy.

4.14. Anthelmintic activity

The methanolic extracts of *S. molle* leaves was evaluated for anthelmintic activity against *Haemonchus contortus* using egg hatch inhibition and adult motility assays (Zenebe et al. 2017). The exposure to the extract (1 mg/mL) inhibited egg hatching efficacy by 96% within 48 hours, compared to albendazole as a standard drug. Moreover, the extract significantly killed the worm adults in concentration and time dependent.

4.15. Hepatoprotective activity

The hepatoprotective effects of *S. polygamus* leaves were reported against CCl_4 -induced liver toxicity (El-Sayed 2016; Mostafa et al. 2018). The oral administration of the ethanol extract significantly diminished the aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP) levels. Furthermore, it increased the level of antioxidant enzymes and glutathione, compared to silymarin and vitamin E.

5. Findings and future prospectives

Extensive research has been displayed to identify the phytochemicals obtained from different Schinus species as well as the pharmacological studies of plant extracts, fractions, essential oils and isolated compounds. Among these species, *S. molle* and *S. terebinthifolius* were found to be the most extensively explored. Unfortunately, some species such as *S. lentiscifolius* and *S. longifolius* are neglected for biological studies. Despite this extensive research, we discovered a few gaps in the experimental or clinical trials. Some studies are recommended to be extrapolated from animal studies to human trials due to the difference in the dose issues, lifespan, anatomy, metabolic

status. There is a great need for well-designed long-term studies in the human subjects for different diseases such as cancer, hepatitis, diabetes mellitus, microbial infections. Also, the researchers have performed a great effort to investigate the underlying mechanism of action for extracts and isolated compounds. Still, there is some biochemical and molecular mechanism warranted be investigated.

6. Conclusion

It was perceived that extensive research work of pharmacological aspects had been done with some species of this genus including *S. molle*, *S. terebinthifolius*, *S. lentiscifolius* and *S. polygamus*; however, some species are still pharmacologically unknown. The phytochemical profile of *Schinus* species mainly consisted of flavonoids, biflavonoids, tannins, catechins, terpenoids and steroids. Convincing traditional evidence are presented alluding to the use of *Schinus* species for bacterial infections, inflammation, ulcer, rheumatism, arthritic disorders, wounds, and high blood pressure. Several studies have revealed the potential of these plants for antibacterial, antifungal, insecticidal, antiparasitic, analgesic, cytotoxic, antitumor, antioxidant, antihypertensive, anti-inflammatory, antimycobacterial, anti-Parkinson, anti-allergic, antiviral, wound healing, chemoprotective, anthelmintic and hepatoprotective activities. All these findings compiled here indicate that the genus may play an important role in the discovery of new medicinal agents. Since its widespread popular use as a medicinal plant, *Schinus* species has shown great potential for the development of new herbal products after assessment of clinical studies and exploration of mechanism of actions for biological activities.

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