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Review Article

Phytochemistry and pharmacological activities of *Saponaria officinalis* L.: A review

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Abstract

Saponaria officinalis is an important medicinal plant cultivated in different parts of the globe for its beautiful flowers. Species is commonly known as soapwort. Central Europe is considered as native place for the species and has been introduced in Northern Asia, West Asia, Northern Europe and America. Plant of the species are perennial, stem erect, branched, leaves ovate or ovate-lanceolate, inflorescence dense cymes, calyx green or reddish, often cleft, petals pink to white, fruit capsules, seeds tuberculate-reniform and numerous per fruit. Indigenous people of different parts of the world use this species to cure various ailments. Traditionally roots of the species have been used as urine remover. It is also used for cough, bronchitis, stomach disorders, bone deformations, rheumatism, pimples, skin diseases, bile disorders, liver problems and respiratory system diseases. The leaves were rubbed on the skin as a repellent and also used as sanitizer, diuretic and in liver diseases. Saporins are ribosome inhibitory proteins and play important role for anticancer properties. Different types of saponins are synthesized by the species exhibit anticancer, antimicrobial, insecticidal and antioxidant properties. The present review is focused on the traditional medicinal uses of species along with phytochemical and pharmacological studies. This review will provide a ground for future research of the species.

Keywords: anticancer; saponaria; saponin; saporin; triterpenoid saponins

Introduction

Saponaria L. is an ornamental plant belonging to the family Caryophyllaceae of angiosperms. This genus is represented by 42 accepted species worldwide (POWO, 2019a). The generic name *Saponaria* was coined by Linnaeus from Greek word '*sapon'* mean 'soap' because roots of some species of the genus were being used as a substitute for soap. This genus belongs to subfamily Caryophylloideae, tribe Caryophylleae of the family Caryophyllaceae (Greenberg and Donoghue, 2011). *Saponaria officinalis* L. is one of the common species of the genus. The specific epithet '*officinalis'* was used in medicine originally for a workshop or shop then herb-store, pharmacy or drug-store (Stearn, 1983). *Bootia saponaria* Neck., *Bootia vulgaris* Neck., *Lychnis officinalis* Scop., *Lychnis saponaria* Jess., *Saponaria hybrida* Mill., *Saponaria officinarum* Rupr. and *Saponaria vulgaris* Pall. are synonyms of the *Saponaria officinalis* (POWO, 2019a). This plant species is commonly known as

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soapwort and cultivated in various parts of the world for its various medicinal properties and beautiful white or pink flowers.

Plants are perennial, stem erect, branched, 30-90 cm; leaves are ovate or ovate-lanceolate, blade strongly 3(-5)-veined. Inflorescence dense cymes. Calyx 15-25 mm, green or reddish, often cleft; petals are pink to white; stamen 10; style 2. Fruit capsules; seeds tuberculate-reniform, numerous per fruit. Species grows on waste places, along stream sides and road sides.

Individual flowers are protandrous and open in the evening and remain open for approximately 72 hours. Development of complete flowers passes through four stages. In the early male phase first whorls of stamens extends from the corolla tube and dehisces. The late male phase is marked by emergence of the second whorl of stamens. The early female phase corresponds to the initial protrusion of the stigmas from the corolla tube. In the late female phase stigmas are curling back towards the petals, anthers are no longer present on the stamens. Study of floral biology on *Saponaria officinalis* indicates that there is a close association between colour change and gender transition in flowers of the species. Moreover, transition from male to female stage in a flower is directly correlated with transition in petal colour, from white to pink. Transition in petal colour in directly related to anthocyanin concentration in the petals. Flowers in female phase are found to have significantly higher anthocyanin concentration than in the male phase. The colour change in flower also corresponded with decrease in male sexual function (pollen grain viability). Colour change in the different parts of the plant is phenotypically plastic. Usually, plants grown in full sun had a more extensive colour change than those grown in shaded areas. But, this property of the plant changes when environmental factors change. Petals are usually wider and longer in female phase flowers compared to male phase flowers (Jabbari *et al.*, 2012; Davis *et al.*, 2014).

Several reviews have been published which deal with medicinal plants of family Caryophyllaceae and their biomedical properties (Arora and Sharma, 2012; Mamadalieva *et al.*, 2014; Chandra and Rawat, 2015; Chandra *et al.*, 2016). But detailed account of medicinal and phytochemical properties is still lacking for this species. The present work is focused on medicinal and phytochemical properties of the species to fill the knowledge gap.

Nativity

Highest diversity of the genus *Saponaria* L. is centred in the temperate Eurasia, chiefly in the Mediterranean and Irano-Turanean region. These areas are considered as centre of origin for this genus (Bittrich, 1993). Central Europe is considered native place for the species *Saponaria officinalis* (Shan-Huah *et al.*, 2010). The species has been introduced in Northern Asia, West Asia, Northern Europe and America (POWO, 2019 b).

Medicinal properties

Leaves, root and whole plant of the species are used to treat various ailments shown in Table 1.

Table 1. Traditional medicinal uses of the *Saponaria officinalis*

Part used	Used in disease	Country	References
Root	It is used as urine remover. It is also a drug for cough, bronchitis, stomach disorders, bone deformations, rheumatism, pimples, skin diseases, bile disorders, liver problems and respiratory system diseases	Turkey	Korkmaz and Ozcelik, 2011
	Acne	Israel	Said *et al.*, 2002
Stem and root	To treat rheumatic pains, as depurative, diuretic and emetic, decoction is taken orally	Morocco	Merzouki *et al.*, 2000
	Rheumatism, respiratory regulation, diuretic	Turkey	Karaman and Kocabas, 2001
Root and leaf	Diaphoretic and tonic. Used for rheumatic diseases, syphilis, tetter, for jaundice and engorgement of the abdominal viscera	Brazil	Medeiros and Albuquerque, 2012
Leaves	Diuretic, bronchitis, expectorant, sudorific	Turkey	Ugulu *et al.*, 2009
	Sanitizer, liver diseases and diuretic	Italy (Sardinia)	Loi *et al.*, 2004
	The leaves were rubbed on the skin as a repellent	(Rome) Italy	Guarrera, 1999
Whole plant	Antialgic	Iberian Peninsula	Anglet *et al.*, 2000
	Constipation, gall disorders, gallstones, haemostatic, common cold, arthritis, rheumatisms, eczema, hair loss, herpes, kidney stones, antipyretic, stimulant.	Greece	Hanlidou *et al.*, 2004
	Skin disease	Italy (Sardinia)	Ballero *et al.*, 2001
	Chopped and applied topically in treatment of all skin diseases	(Campania) Italy	Novella *et al.*, 2013

Ribosome inactivating proteins

Ribosome-inactivating proteins (RIPs) are the plant proteins that enzymatically damage ribosomes in a catalytic manner, thus inhibiting protein synthesis. RIPs inhibit protein synthesis by depurinating an adenine residue present in a conserved stem-loop region of 23/26/28S ribosomal RNA (rRNA) and ultimately removal of adenine, thereby causing an irreversible arrest in protein synthesis (Lombardi *et al.*, 2010). RIPs can eliminate adenines from any kind of nucleic acid namely rRNA, tRNA, mRNA, viral RNA and even DNA. Such activity of RIPs is lead to rename with the more significant and systematic denomination of adenine polynucleotide glycosylases (Girbes *et al.*, 2004). RIPs are present in a large number of plants species and also have been detected from fungi, algae and bacteria. First identified RIPs were ricin and abrin from the seeds of *Ricinus communis* and *Abrus precatorius* respectively (Stirpe, 2004). The angiosperm families *i.e.* Caryophyllaceae, Sambucaceae, Cucurbitaceae, Euphorbiaceae, Phytolacaceae and Poaceae show high RIPs activity (Girbes *et al.*, 2004).

RIPs are present in multiple forms and have been classified as type 1 RIP consists of single chain, strongly basic proteins, having enzymatic activity. They inhibit cell-free protein synthesis but are relatively non-toxic to cells and animals. Saporin from *Saponaria officinalis,* trichoanguin from *Trichosanthes cucumerina*, momordin I and momordin II from *Momordica charantia* are examples of this category. Type 2 RIPs consist in enzymatic chain A similar to type 1 RIPs which is linked to a slightly larger chain B. Chain B is a lectin specific for sugars generally with the terminal free D galactose structure. In type 2 RIPs chain B binds to cell membranes facilitating the entry of chain A into the cell. Inside the cell, chain A damage ribosomes which cause subsequent cell death. This group includes ricin, abrin and other potent toxins. Type 1 RIPs are less toxic as compare to type 2 RIPs because they lack B-chain and do not enter inside the cell. However, they can be toxic if they are conjugated to molecules capable to deliver RIPs type 1 into the cell. Third type of RIPs, type 3 RIPs also has been proposed which synthesized as a proenzyme and activated after the removal of a short internal peptide segment. Maize b-32 RIP is example of type 3 RIPs and activated after the removal of a short internal peptide segment (Girbes *et al*., 2004; Stirpe, 2013).

Saporins are type 1 RIPs extracted from different tissues of the soapwort plant. The saporin was detected and examined in leaves, stems, roots, flowers, and fruits except immature seeds (Ferreras *et al*., 1993). High levels of activity were found in roots and mature seeds and leaves despite of being old or young leaves. Saporin expression also has been studied in callus, cell suspensions, and root cultures from soapwort explants. The highest activity was found in callus extracts and lower levels were reported in the root extracts (Di Cola *et al*., 1997). An isoform 6 of saporin (SO6) has been isolated from the seeds of *Saponaria officinalis.* Savino *et al.* (2000) studied crystal structure of SO6 and its interaction with ribosomes. They concluded that SO6 is made up of two domains, the N-terminal domain which is predominated by six β-sheets and the C-terminal domain which is predominated by eight α-helices (Figure 1). The contact surface of SO6 with ribosome is present inside the C-terminal region.

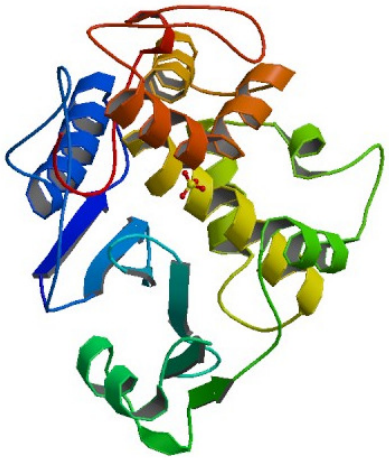


Figure1. Crystal structure of saporin SO6 (https://doi.org/10.2210/pdb1QI7/pdb)
(Source: RCSB PDB)

Saporin-L1 (SAP) is another RIP type 1 saporin isolated from *Saponaria officinalis* (soapwort) leaves. It is homologue of ricin A-chain (RTA). RTA is the catalytic subunit of RIP ricin. SAP exhibits N-glycohydrolase activities on 80S ribosomes, poly (A) RNA, and other cellular DNA and RNAs. It releases multiple adenines from ribosomes (Ho *et al*., 2009). SAP is a monomer with two domains: N-terminal with β-sheet with a short intervening α -helix and a C-terminal contains α helical cluster that is followed by antiparallel β-sheet (Figure 2).

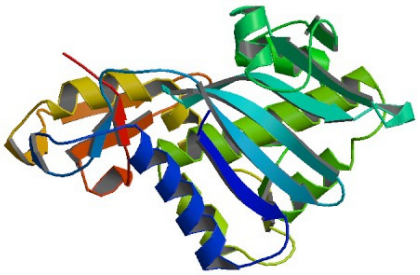


Figure 2. Crystal structure of Saporin-L1 (https://doi.org/10.2210/pdb3HIS/pdb) (Source: RCSB PDB)

Saponins

The term saponin derived from the Latin (Greek?) word *sapo*, which means 'soap'. These characterized by forming foams when shaken with water and chemically referred as tri-terpene and steroid glycosides. Saponins consist of nonpolar aglycones coupled with one or more monosaccharide moieties. This combination of polar and non-polar structural elements in saponins explains their soap-like properties in aqueous solutions (Vincken *et al.*, 2007). Saponins are made up of two components: aglycone and a sugar moiety. The two components are linked at C-3 between aglycone and a sugar chain via glycosidic linkage (El Aziz *et al.*, 2019). Saponins are classified on the basis of their aglycone or sapogenin skeleton into two groups. The first group characterized by presence of steroidal saponins and second group characterized by presence of the triterpenoid saponins. The steroidal saponins are mainly found in monocotyledons while, triterpenoid saponins occur mainly in the dicotyledons (Sparg *et al.*, 2004; Man *et al.*, 2010). Triterpene saponins are found in the Caryophyllaceae family (Bottger and Melzig, 2011). Basic structure of the triterpene is 30 carbons, which is made derived from three monoterpenes (10 carbon atoms) (Rahimi *et al.*, 2019). On the basis of the number of sugar moieties linked to the aglycone nucleus, triterpenoid saponins are further classified into two groups: monodesmosidic and didesmosidic. In the monodesmosidic triterpenoid a single sugar chain is attached at C-3. In the bidesmosidic triterpenoid two sugar chains are attached: one at C-3 (ether linkage) and other at C-28 (ester linkage) or at C-24 (ether linkage) (El Aziz *et al.*, 2019). In *S. offcinalis* four aglycones hederagenin, hydroxyhederagenin, gypsogenin and quillaic acid are found and form the triterpenoid glycosides; they are mostly bisdesmosides (Smułek *et al.*, 2017) Figures 3 and 4.

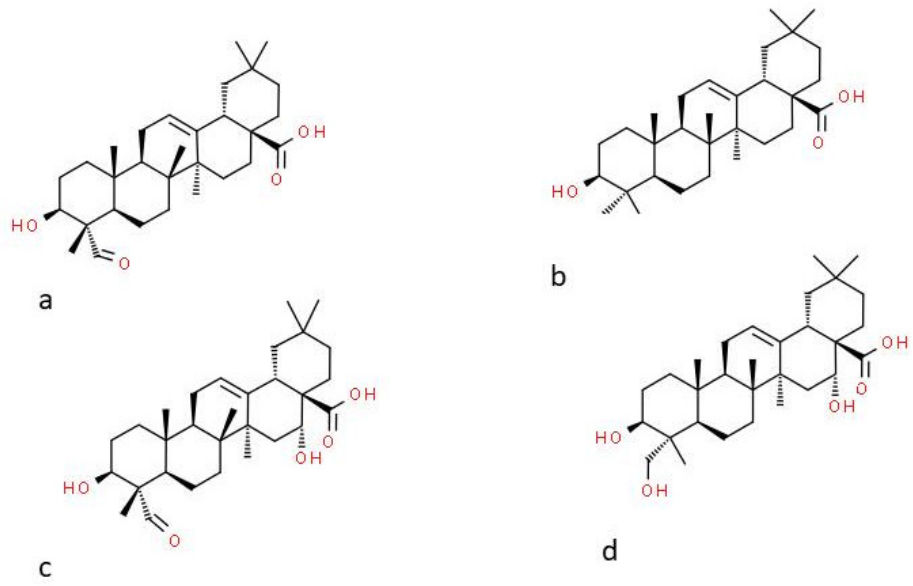
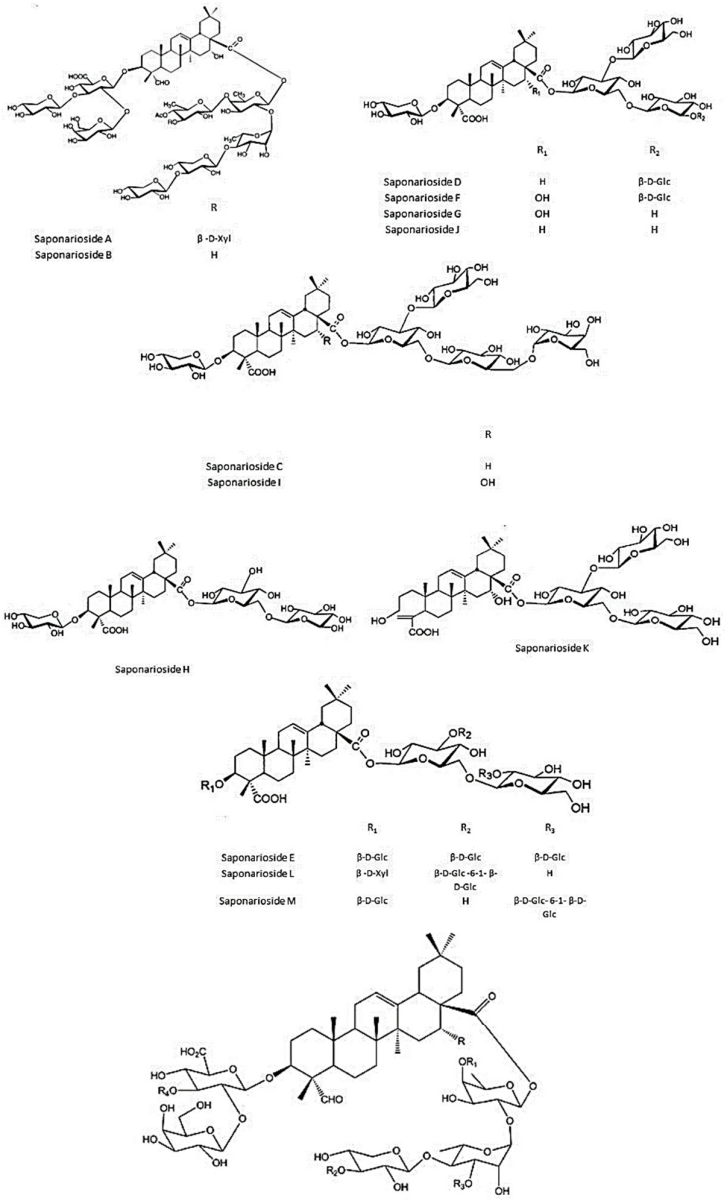


Figure 3. Aglycones structure (a: gypsogenin, b: hederagenin, c: quillaic acid, d: hydroxyhederagenin) (Source: www.chemspider.com)

Jia *et al.* (1998) isolated saponariosides A-B, Jia *et al.* (1999) isolated saponarioside C-H and Koike *et al.* (1999) isolated saponarioside I-M from the whole plant of *S. officinalis*. Moniuszko-Szajwaj *et al.* (2013) isolated vaccaroside D and dianchinenoside B, saponarioside C, D, F, G, I, K, L, hydroxygypsogenic acid derivative compound 1-2 and gypsogenic acid derivative compound 3 from the roots. Lu *et al.* (2015) isolated quillaic acid derivative compound 1-9 and gypsogenin derivative compound 10-14 from the roots.



	R
Saponarioside A	β -D-Xyl
Saponarioside B	H

	R_1	R_2
Saponarioside D	H	β-D-Glc
Saponarioside F	OH	β-D-Glc
Saponarioside G	OH	H
Saponarioside J	H	H

	R
Saponarioside C	H
Saponarioside I	OH

Saponarioside H

Saponarioside K

	R_1	R_2	R_3
Saponarioside E	β-D-Glc	β-D-Glc	β-D-Glc
Saponarioside L	β -D-Xyl	β-D-Glc -6-1- β-D-Glc	H
Saponarioside M	β-D-Glc	H	β-D-Glc- 6-1- β-D-Glc

	R	R1	R2	R3	R4
Compound 1	OH	H	H	β -D-Glc	β -D-Xyl
Compound 2	OH	H	H	6-OAc- β-D-Glc	β -D-Xyl
Compound 3	OH	H	β -D-Xyl	β-D-Glc	β -D-Xyl
Compound 4	OH	H	β -D-Xyl	6-OAc- β-D-Glc	β -D-Xyl
Compound 5	OH	α -D- Gal	H	β-D-Glc	β -D-Xyl
Compound 6	OH	α -D- Gal	H	6-OAc- β-D-Glc	β -D-Xyl
Compound 7	OH	α -D- Gal	β -D-Xyl	β-D-Glc	β -D-Xyl
Compound 8	OH	H	H	β-D-Glc	α -L-Gal-(1→4)- β -D-Xyl
Compound 9	OH	H	H	6-OAc- β-D-Glc	α -L-Ara
Compound 10	H	H	H	β-D-Glc	β -D-Xyl
Compound 11	H	H	H	6-OAc- β-D-Glc	β -D-Xyl
Compound 12	H	H	β -D-Xyl	β-D-Glc	β -D-Xyl
Compound 13	H	H	β -D-Xyl	6-OAc- β-D-Glc	β -D-Xyl
Compound 14	H	H	β -D-Xyl	H	β -D-Xyl

Figure 4. Structure of saponins of *Saponaria officinalis*
Source: Jia *et al.* (1998, 1999), Koike *et al.* (1999), Moniuszko-Szajwaj *et al.* (2013), Lu *et al.* (2015)

Floral scent composition of *Saponaria officinalis*

Floral scent composition of *Saponaria officinalis* was studied by Jurgens *et al.* (2003). The floral scent of this species is dominated by methylbenzoate which is accounted for 68.7% of the total scent. Apart from this fatty acid, its derivatives n-hexanal, n-heptanal, n-octanal, n-nonanal, n-decanal. Benzenoids derivatives, methylbenzene and 1,2-dimethylbenzene are also present (Jurgens *et al.*, 2003).

Essential oil composition

Phytochemical analysis of essential oil obtained from the fresh flowers and shoots was done by Petrović *et al.* (2017). They isolated 87 compounds including phytol, tricosane-6,8-dione, patchouli alcohol from the shoot and 66 compounds including patchouli alcohol, heneicosane and tricosane from the flowers. They further elucidated that non-terpenoid compounds contribute higher in the essential oil of shoots, while oxygenated sesquiterpenoid and non-terpenoid compounds are present equally in the flower oil.

Saporin as anticancer agents

Several studies have revealed anticancer properties of saporin-S6 by causing necrosis and apoptosis in pre-clinical models of various human cancer cells. Initially, these properties of saporin-S6 were considered due to the ability of these molecules to inhibit protein synthesis. However, many observations revealed that RIPs can also depurinate DNA and other nucleic acids. Saporin-S6 is able to kill cells via apoptosis (Bergamaschi *et al.*, 1996; Bolognesi *et al.*, 1996). Saporin-S6 induces apoptosis in caspase-dependent manner in U937 cells through a mitochondrial cascade, independently of translation inhibition. These proteins induce apoptosis via activation of caspase 9. Extrinsic pathway of apoptosis is not involved in saporin-S6-induced mediated apoptosis of U937 cells because caspase 8 and truncated Bid are not activated in this process (Sikriwal *et al.*, 2008), while, in the case of L540 lymphoma cells, both caspase 9 and 8 are activated by saporin-S6 (Polito, *et al.*, 2009). In the U87 glioblastoma cell line saporin-S6 treatment leads the activate ERK 1/2 (mitogen activated protein kinase) instead of caspase 8 and 9. Activation of ERK1/2 might cause cell cycle arrest in G1 phase with a decrease in D1 cyclin levels and causes apoptosis (might be due to activation of p53) (Cimini *et al.*, 2012; Polito *et al.*, 2013).

Gilabert-Oriol *et al.* (2016) reported that saporin SO1861 from *S. officinalis* increases the cytotoxicity of saporin without affecting its enzymatic activity. It was also found when immunotoxin saporin-rituximab was applied in the cells (human B-cell Burkitt lymphoma cells) with nontoxic concentration of the SO1861 the cytotoxicity increases to 700fold. Combinatorial use of SO1861 augments therapeutic potential of Rituximab-immunotoxins against B-cell lymphoma. SO1861 does so, by modifying trafficking of immunotoxins and inhibiting their degradation in lysosome and consequently increase their concentration in cytosol to inactivate ribosomes. Due to inactivation of ribosomes, protein synthesis stops and cell enter for apoptosis (Gilabert-Oriol *et al.*, 2016).

Antioxidant properties

Lipid peroxidation is described as a process under which oxidants (free radicals or non radicals) attack lipids containing carbon double bonds. Consequent abstraction of hydrogen from carbon and insertion of oxygen form lipid free radicals and hydroperoxides. Membrane phospholipids are major targets of oxidative damage; hence lipid peroxidation is often the first parameter analysed for proving the involvement of free radical damage. Malondialdehyde (MDA) is one of the products of lipid peroxidation and it is widely used as marker for lipid peroxidation. MDA is the most mutagenic product of lipid peroxidation and can react with proteins and DNA (Ayal *et al.*, 2014). Furthermore, presence of MDA is considered as an indicator of free-

radical damage through membrane lipid peroxidation. Antioxidant activity of *Saponaria officinalis* was observed in X rays irradiated rats and found that 100 mg/kg extract markedly depressed the oxidant concentrations by 20.8% on day 21 and by 30.6% on day 42. Consequently, the plasma MDA concentrations decreased in X rays irradiated rats treated with the plant extract (Kucukkurt *et al.*, 2011). Plant extract exhibited directly reduce basal MDA formation and show antioxidant properties towards ionizing radiation-induced cell damage. Increase percentages of the antioxidant activity in plant extract treated rats marked with increases in the circulating vitamin C concentrations compared to the only irradiated controls. However, Deger *et al.* (2003) found that vitamins C and vitamins E do not affect initial values of MDA concentrations in rabbits after exposure to X-rays. Decreases in MDA concentrations in *Saponaria officinalis* treated rats could be due to the ability of extract to scavenge secondary reactive radicals and prevent formation of superoxide, hydrogen peroxide in response to the radiation treatment (Kucukkurt *et al.*, 2011).

Antioxidant activity of the methanol extracts of *Saponaria officinalis* was determined according to the *β*-carotene bleaching method by Sengul *et al.* (2011). The results pointed that plant extract showed antioxidant activity (70.00%) which was less than standard Butylated hydroxyanisole (BHA) (93.21%) and Butylated hydroxytoluene (BHT) (90.71%). There is strong relationship between the total phenolic content and antioxidant activity in certain plants. In the *Saponaria officinalis* the phenolic content is 6.57 μg gallic acid equivalent (GAE)/mg, reported by Sengul *et al.* (2011).

Anti-microbial properties

Methanol extract of *S. officinalis* exhibit antimicrobial properties against *Bacillus subtilis*, *Staphylococcus aureus*, *Salmonella typmiruim*, *Candida albicans*, *Streptococcus thermophilus*, *Pseudomonas aeruginosa*, *Klebsiella pneumonia* subsp. *pneumonia*, *Staphylococcus hominis*, *Enterobacter cloaceae*, *Escherichia coli*, *Proteus mirabilis*, *Klebsiella pneumonia* subsp. *ozanae*, *Providencia alcaliaciens*, *Acinetobacter lwoffi*, *Pseudomonas fluorescens*, *Pseudomonas putida*, *Yersinia enterocolitica* and *Penicillium brevicompactum*, while, aqueous of the plant exhibited antimicrobial activities against *Flavobacterium indologenes* (Sengul *et al.*, 2011). The root extract of *S. officinalis* shows antifungal activities against *Candida albicans* (Sadowska *et al.*, 2014). Exact mechanism of anti-microbial properties is not yet known but, it is postulated that saponins play an important role as ant-microbial compounds (Nabinejad, 2013).

Other miscellaneous properties

The hepatoprotective effect of *S. officinalis* roots was evaluated on mice model. The study revealed that the soapworts supplementation reduced the damaging effects on the liver by carbon tetrachloride (CCl_4). Exact mechanism of this property is yet not elucidated, but it is postulated that CCl_4 harm liver functioning by enhancing lipid peroxidation. Thus, root extract of *S. officinalis* might detoxify the free radicals produced following CCl_4 intoxication and enhance liver functioning (Rahman and Megeid, 2006). The saponin rich extract of *S. officinalis* probably do not remove lipids from the outer most layer of human skin epidermis (stratum corneum) (Jurek *et al.*, 2019). *Tetranychus urticae* Koch. a two-spotted spider mite is one of the most harmful pests. It is phytophagous, feeds on field crops and greenhouse ornamentals including more than 1100 plant species. In greenhouse-grown plants, 30-gram root extract of *S. officinalis* in 1 litre water for about 25 min significantly reduce all developmental stages of the two spotted spider mites (Pavela, 2017; Pavela *et al.*, 2017).

Conclusions

Saponaria officinalis is an important medicinal and ornamental plant. Different saporins found in the species cause cytotoxicity of various cell lines and thereby play an important role in cancer treatment. Various

kinds of saponins are synthesized by the species and exhibit anticancer, antimicrobial, antioxidant and anti-insecticide properties. Further studies need to be done for anticancer properties of the saponins and saporins of the species for proper understanding of their target-receptor mechanism and scientific evaluation of traditional medicinal uses.

Authors' Contributions

SC: hypothesized and drafted the manuscript. DSR: guided drafting of the manuscript. AB: helped in the drafting. All authors read and approved the final manuscript.

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Conflict of Interests

The authors declare that there are no conflicts of interest related to this article.

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