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A comprehensive review on the botany, traditional uses, phytochemistry, pharmacology and toxicity of *Anagallis arvensis* (L).: A wild edible medicinal food plant

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ABSTRACT

Medicinal plants, since times immemorial, have been used in virtually all cultures for therapeutic purposes. *Anagallis arvensis* (L.) is a well-known medicinal plant traditionally utilized for a varied range of disorders including wound healing, lung problems, kidney stones, urinary tract infections, gout, and rheumatic conditions. This review is an attempt to summarize and comprehend the fragmented information until now published in the literature on the biochemical and toxicological perspective of *A. arvensis*. The literature was searched electronically from PubMed, EMBASE, Scopus, Science Direct, Ovid MEDLINE and Google Scholar. It was found that ethnomedical uses of *A. arvensis* plant and parts have been recorded throughout the world, where it has been used against a panoply of diseases. Phytochemical search has led to the identification of flavonoids, terpenoids, triterpenoid glycosides, phytosterols as main classes of secondary metabolites with a few other classes. A wide spectrum of *in vivo* and *in vitro* pharmacological activities have been reported from fresh plant material and its crude extracts and/or fractions. However there is currently a dearth of structure-activity studies of the isolated compounds and mechanistic studies from this species. The plant has also been reported for *in vivo* toxicity. It is clear from this review that*A. arvensis,* though traditionally used by various cultures harbour a plethora of bioactive compounds exhibiting multifarious biological effects that could be exploited as biopharmaceuticals. Noentheless, additional research work and structure-activity studies arekey prerequisite to transmute the empirical claims on the utilization of *A. arvenisis* in folklore medicines and a food plant into scientific shreds of evidence.

1. Introduction

In recent years, there has been a growing global interest in herbal medicines and related products sourced from local medicinal plants and herbs (Joubert, De Beer, & Malherbe, 2017; Qasim et al., 2017). Ethno-pharmacology is the first approach for investigating natural resource management of native society. It is a science of human synergy with plants and ecosystems (Ahmad, Jantan, & Bukhari, 2016). For more than 100 years, plants are being used for different therapeutic purposes and recently there is a renewed interest to scientifically validate the folklore uses of these medicinal plants (Khoshkholgh-Pahlaviani et al., 2013). This traditional information has been vocally disclosed from generation after generation; hence these folklore therapies are still in exercise. The understandings of traditional healing practices, gathered by trial and error over hundreds of years employing the patient as an investigational animal all the way through, necessarily enclose some scientific merit that is worth of investigation. In consequence, experimental data on such medicinal plants is a prereq-

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uisite in order to confirm the claims of the traditional medicinal system (Ahmad et al., 2016).

The genus *Anagallis* belongs to family Primulaceae which is reported to have about 1000 species with 22 genera, further subdivided into five different tribes as primuleae, cyclamineae, lysimachieae, samoleae and corideae. *Anagallis* belongs to lysimachieae tribe, which further comprises about 28 species (Sayanova, Napier, & Shewry, 1999). The family Primulaceae is famous because of being active for many skin complications, and the plant species of this family are enriched with many vital phytoconstituents like triterpene saponins, flavonoid and phenolic glycosides (John, 1978, Akerreta, Cavero, López, & Calvo, 2007). Plants of this family have been reported to exhibit many other pharmacological activities including skin problems, antigenic, expectorant, anti-bacterial, diuretic, antioxidant, antimicrobial, antiviral, antifungal, antimutagenic, cytotoxic, anticancer, anti-leishmaniasis, and dermatological activities (Yamada, Hagiwara, Iguchi, Takahasi, & Hsu, 1978, Kshirsagar & Singh, 2001; Morozowska & Wesołowska, 2004, Akerreta et al., 2007, Bhatia, Sharma, Manhas, & Kumar, 2014). *Anagallis arvensis (A. arvensis)*, one of the important perennial or annual medicinal plants of this genus, widely distributed throughout the world is of ethnobotanical importance regarding wound healing activities (Al-Snafi, 2015). The most common synonym for *A. arvensis* is *Lysimachia arvensis* (Manns & Anderberg, 2009). This genus has a common feature of the flowering pattern as they are pentamerous, nectarless, polypetalous and have a compound ovary (Gibbs & Talavera, 2001). The taxonomical classification of *A. arvensis* is given in Table 1.

The aerial parts of this plant are used traditionally to make an ointment for treating external infections, including infected pimples and wounds. The plant is also reported to be used as diuretic, diaphoretic, expectorant, rheumatism, hepatic and renal complaints, epileptic attacks, mania, oedema, antifungal, and anti-inflammatory agent (Akerreta et al., 2007; Lopez, Akerreta et al., 2008; Sundaram, Singh et al. 2010; López, Cavero, & Calvo, 2013; Salam, Ahmed, & Ali, 2011; Gulshan, Dasti, Hussain, Atta, & Amin-ud-Din, 2012; Sharifi-Rad et al., 2016). The effects of *A. arvensis* crude extract and its (aqueous and organic) portions on spasmogenic, spasmolytic, bronchorelaxant, and hypotensive folkloric usage have been established along *via in vitro* testing on isolated jejunum, ileum, trachea, aorta, paired atria preparations, and *in vivo* in mice and normotensive anaesthetized rats (Saqib & Janbaz, 2021).

Pastoriza, Sgariglia, Soberón, and Sampietro (2022), has published a mini-review on chemical composition and pharmacological activities of *A. arvensis* (Al-Snafi, 2015), and still there is a need of an up-to date detailed review for this pant. Thus, the present review was carried out to furnish an updated and thorough outline of the botanical aspects, phytochemical composition, traditional claims, pharmacological effects, and toxicity of different parts of *A. arvensis*. Furthermore, the current information acquired primarily from scientific studies, then thoroughly and critically evaluated to deliver confirmations and validations for local and traditional uses of *A. arvensis* and also to recommend imminent research projections and probable beneficial usages of this plant. The present document will provide support in its usage and further exploration of new drugs discovery from natural products.

Table 1
Taxonomic classification of *A. arvensis*.

Taxonomic classification	
Kingdom	Plantae
Phylum	Angiosperm
Class	Eudicots
Subclass	Astrids
Order	Aricales
Family	Primulaceae
Genus	*Anagallis*
Specie	*Arvensis*

2. Results and discussion

2.1. Vernacular names

Anagallis arvensis is known by different vernacular names in different countries (Table 2).

2.2. Distribution and botanical description

It is a perennial or annual plant, without rosettes, not stoloniferous; stems are creeping to erect weakly, 5–30 cm long, glabrous, angular with four longitudinal keels. Leaves opposite, ovate to oblong-ovate, occasionally narrowly so, usually 5–25 mm long; sessile. Corolla 5-lobed, 5–12 mm diam., red, pink, orange or blue filaments villous with multicellular hairs, staminodes are lacking (Al-Snafi, 2015). It is widely distributed throughout the world, being found in all temperate regions in both hemispheres including Europe, Asia, United States and non-tropical South America (Salam et al., 2011; Sharifi-Rad et al., 2016). The picture gallery of *A. arvensis* is presented in Fig. 1.

2.3. Traditional uses

The traditional usage of *A. arvensis* includes the antitussive, purgative, cholagogue, diuretic, expectorant, diaphoretic, nervine, and stimulant properties (Launert, 1981). In Taiwan, the whole herb

Table 2
Vernacular names of *A. arvensis*.

Country	Vernacular name	Country	Vernacular name
Algeria	Lizireg, Meridjana	Brazil	Escalarte, Chile, Pimpinelaazul
Croatia	Krikapoljska	Czechoslovakia	Drchnickaroini
Denmark	Rod arve	Egypt	Ommlebben, Qonfooda, Saboongheit
Finland	Punaalpi	French	Morgeline, Mouron des champ, Mouron rouge
Germany	Acker gauchheil, Feldgauchheil, Rotergauchheil	Hawaii	Poisonous pimpernel
Hungary	Mezeltikszem	India	Biliputi, Krishnaneel
Iran	Bazrakvahshee	Iraq	Ayen el Jamel, Rmaimeeneh
Italy	Anagalliderossa, Bellichina, Mordigallina	Japan	kabanaarurihakobea
Kannada	Suryakantisoppu	Lebanon	Adhan nabti, Lubbay, Zaghila
Macedonia	Vidovcicacrvena	Malayalam	Bellichina
Marathi:	Ran draksh	Mauritius	Mouron
Netherlands	Gewoonguichelheil, Guichelheil	Norway	Nonsblom, Rodarve
Pakistan	Bilibooti	Poland	Kurzysladpolny
Portuguese	Escarlate, Morriaovermelho, Murriao	Slovenia	Njivnakurjacesnjica
South Africa	Blouseblommetjie, Rooimuur	Spanish	Pimpinela, Pimpinelaescarlata Pimpinelarosada
Sweden	Rodarv, Roedarv	Taiwan	Hwo-jin-gu
Serbia	Vidovcia	Montenegro	Vidovcia
Turkey	Tarlafarekulagi	Urdu	Billibooti
USA	Poison chickweed, Poisonweed, Shepherd's clock	Yugoslavia	Vidovcia

Fig. 1. (A) Whole plant of *A. arvensis* (B) leaves of *A. arvensis* (C) flowers of *A. arvensis*.

of *A. arvensis* is used for liver complications (Yamada et al., 1978). In veterinary uses, *A. arvensis* is used for curing mastitis because of anti-inflammatory and emollient properties (Viegi, Pieroni, Guarrera, & Vangelisti, 2003). A slurry of leaf part is used for removing the leeches from cattle's nostrils (Bhatia et al., 2014). In humans as well as in veterinary, the plant used for wound healing applications. Different types of pharmaceutical dosage forms, including ointments and infusions, were prepared to get both local and systemic benefits from the plant (López, Cavero, & Calvo, 2013). In Nepal, people from rural areas use this plant as a piscicidal agent. For the poisoning of fish, they used the whole plant, crush it and disperse it in the river (Karki, 1982). Pelotaris of Bosque area used ointments for healing wounds of hands after their matches. *A. arvensis* has widespread use for skin diseases (Akerreta et al., 2007). Seeds and herb used as sudorific and in rabies (Raju & Rao, 2012). As a traditional north-western medicine, the plant is used in treating fungal infections in Argentina (Rondina, Bandoni, & Coussio, 2010; Middleditch, 2012). In European folk medicine, it was once used as a medicinal herb for treating gallstones, cirrhosis, lung problems, kidney stones, urinary tract infections, dropsy, gout and rheumatic conditions (Barker, 2001; Bown, 1995; Hensel, 2008; Stuart, 1979). Itchy skins and warts can be treated by a homoeopathic formulation made by *A. arvensis* (Launert, 1981). In Indian medicine, this plant has reported being used for menstruation disorders. Likewise, in homoeopathic medicine system, it is used in the treatment of skin rashes, warts and urinary tract infections (Gruenwald, 2000). The traditional use of *A. arvensis* in different countries, along with the parts used, are summarized in Table 3.

2.4. Phytochemistry

Plants are comprised of numerous metabolic products, of them energy is derived from primary metabolites, while the specialized functions like plant defence are governed by secondary metabolites. Alkaloids, flavonoids, terpenoids, glycosides, steroids and fatty acids are among the groups of secondary metabolites. The medicinal properties that a plant may possess are primarily due to the presence of these secondary metabolites (Evans, 2009).

Table 3
Traditional uses of *A. Arvensis.*

Country	Part	Traditional uses	Ref
Taiwan	WP	Liver complications	(Yamada et al., 1978)
Chinese medicine	H	Snake bites, Dog bites, Joint ailments, Oedema	Gruenwald (2000)
Spain	AP	Respiratory infections, Infected spot	(Lopez, Akerreta et al., 2008)
Argentinean north-western	WP	Fungal infections	(Rondina et al., 2010)
Nepal	WP	Piscicidal agent	Karki (1982)
Indian medicine		Menstruation disorders	Gruenwald (2000)
European folk medicine	WP	Treating gallstones, Cirrhosis, Lung problems, Kidney stones, Urinary tract infection, Dropsy, Gout, Rheumatic conditions	(Barker, 2001; Bown, 1995; Hensel, 2008; Stuart, 1979)

WP: whole plant; H: herb; AP: aerial parts.

Anagallis arvesnsis belongs to family primulacae. It is a summer annual herb distributed worldwide or with a global spread abundantly found in Egypt, Palestine, a non-tropical region of South America, Taiwan, and India (more specifically Jammu & Kashmir). Different parts of plant contain variety of active constituents; such as glycosides, saponin, flavonoid, anthraquinone, alkaloids, rutin, kaempferol, oleanane triterpenes, anagalligenin, anagalligenone, stigasetrol, arvenin I, arvenin II, cucurbitacin B, D, E, I,L& Q, nhexosamine, β-amyrin, sterols carbohydrates, lacceric acid. *Anagallis arvensis* has recognized medicinal values as an anti-mycotic, antimicrobial, molluscicidal, antioxidant, anti-inflammatory, antileishmania, antiviral, cytotoxic, and spermatogenesis. The present review will highlight the traditional uses, phytoconstituents and pharmacological effects of *Anagallis arvensis* (Yasmeen, Basit, & Tahir, 2020).

UHPLC-ESI-QTOF-MS/MS and nuclear magnetic resonance (NMR) analyses were used to chemically analyse a triterpenoid saponin-rich fraction (F4) of *A. arvensis*. Findings suggested the existence of nine monodesmosidic saponins and added to our understanding of the cytotoxic effects of *A. arvensis* and the phytochemistry of its triterpenoid saponins (Pastoriza, Sgariglia, Soberón, & Sampietro, 2022). Due to the presence of antioxidant phytochemicals, as recorded from GC-MS analysis, it was inferred that *A. arvensis* might operate as uroprotective and hepatoprotective in the rodent model. Future research must focus on isolating the active phytochemical components of the methanol extract of *A. arvensis* and determining their precise mode of action(Shabbir et al., 2022) (Saleem et al., 2020).

Another study explored the phytochemical make-up and enzyme-inhibiting capabilities of *A. arvensis*. HPLC-PDA polyphenol quantification and UHPLC-MS analysis to determine the phytochemical profile, along with *in vitro* assays to determine the enzymes' inhibitory activity against amylase and tyrosinase were done. Catechin, gallic acid, chlorogenic acid, and ferulic acid were among the polyphenols detected by HPLC-PDA polyphenolic quantification, and 34 secondary metabolites were provisionally identified by UHPLC-MS in both DCM extracts. All of the extracts dsiplayed weak amylase inhibition and moderate tyrosinase inhibition. Although secondary metabolites were only tentatively identified by its UHPLC-MS profiling, the aerial-DCM extract demonstrated relatively stronger tyrosinase and amylase enzyme inhibitory potential (Saleem, Zengin, Locatelli, Abidin, & Ahemad, 2022). which could be justified by the presence of the polyphenols present.

A very fewer phytochemical studies have been carried out, and about 55 secondary metabolite compounds have been isolated from the different parts of *A. arvensis*, which belong to flavonoids, triterpenoids and steroids class (Table 4). Among these isolated compounds flavonoids, triterpenoids and their glycosides are the characteristic compounds of *A. arvensis.* The presences of a specific category of compounds make this plant more important concerning its use in phytopharmaceutical products and industrial applications. The details regarding isolation/identification of these phytochemicals from *A. arvensis* are given below:

2.4.1. Flavonoids

Flavonoids are important secondary metabolites from plants. The phenolic and flavonoid compounds, consisting of an aromatic ring with hydroxyl groups, are the reason why a plant may possess a strong antioxidant capacity. The prevention and cure of various disorders like cancer, cardiovascular diseases, neurodegenerative disorders, and aging, etc., have a direct link to the presence of flavonoids

Table 4
Chemical group, part of plant studied and chemical constituents isolated from *A. arvensis*.

No	Chemical group	Part	Ref.
	FLAVONE AND FLAVONE GLYCOSIDES		
1	Kaempferol 3-glucuronide (flavonoid glycoside)	WP	(Kawashty et al., 1998)
2	Kaempferol 7-glucoside (flavonoid glucoside)	WP	(Kawashty et al., 1998)
3	Kaempferol 3-glucuronosyl glucoside	WP	(Kawashty et al., 1998)
4	Kaempferol 3, 7-diglucoside	WP	(Kawashty et al., 1998)
5	Quercetin 3- glucuronide	WP	(Kawashty et al., 1998)
6	Quercetin 3- glucoside	WP	(Kawashty et al., 1998)
7	Quercetin 7- glucoside	WP	(Kawashty et al., 1998)
8	Quercetin 3-glucuronosyl glucoside	WP	(Kawashty et al., 1998)
9	Quercetin 3-glucuronide 3-glucoside	WP	(Kawashty et al., 1998)
10	Quercetin 3, 7- diglucoside	WP	(Kawashty et al., 1998)
11	Isorhamnetin 3-glucuronide	WP	(Kawashty et al., 1998)
12	Isorhamnetin 3-glucuronosyl-glucoside	WP	(Kawashty et al., 1998)
13	Isorhamnetin 3-galactosyl-glucoside	WP	Ishikura (1981)
14	Malvidin 3-rhamnoside	WP	Ishikura (1981)
15	Luteolin (Flavone)	WP	Ishikura (1981)
16	Luteolin 7-glucoside	WP	Ishikura (1981)
17	Quercetin 3-rhamnoside	WP	Ishikura (1981)
18	Rutin (Flavonoid glycoside)	A	(Asolkar & Chopra, 1992, Yusuf et al., 1994)
19	Malvidin 3- glucoside	WP	(Harborne, 1968, Kawashty et al., 1998)
20	Pelargonidin	WP	(Harborne, 1968, Kawashty et al., 1998)
	TRITERPENOIDS		
21	Arvenin I (2-*O*-β-D-glucopyranosyl Cucurbitacin B)	WP	(Yamada et al., 1977)
22	Arvenin II (2-*O*-β-D-glucopyranosyl 23,24-dihydro-Cucurbitacin B)	WP	(Yamada et al., 1977)
23	Arvenin III (2-*O*-β-D-glucopyranosyl Cucurbitacin D)	WP	(Yamada et al., 1978)
24	Arvenin IV (2-*O*-β-D-glucopyranosyl 23,24-dihydro-Cucurbitacin R)	WP	(Yamada et al., 1978)
25	Dihydrocucurbitacin B		(Cai, Fang et al. 2015)
26	Cucurbitacin B		(Cai, Fang et al. 2015)
27	Cucurbitacin D		(Cai, Fang et al. 2015)
28	Cucurbitacin E		(Cai, Fang et al. 2015)
29	Cucurbitacin I		(Cai, Fang et al. 2015)
30	Cucurbitacin L		(Cai, Fang et al. 2015)
31	Cucurbitacin Q		(Cai, Fang et al. 2015)
32	Anagalligenin B 3-0-{β-D-xylopyranosyl (1 → 2) -β-D-glucopyranosyl (1 → 4)-[β-D-glucopyranosyl-(1 → 4)-β-D-glucopyranosyl (1 → 2)]-α-L-arabinopyranoside}	WP	(Mahato, Sahu et al. 1991)
33	Anagalligenone 3-0-{β-D-xylopyranosyl (1ar2)-β-D-glucopyranosyl (1ar2)-β-D-glucopyranosyl(1ar4)-[β-D glucopyranosyl(1 → 2)]-α-L arabinopyranoside}	WP	(Mahato, Sahu et al. 1991)
34	Anagalligenone 3-0-{β-D-xylopyranosyl (1 ar 2)-α-D-glucopyranosyl (a ar 4)-[β-D-glucopyranosyl-(1ar2)]-α-L-arabinopyranoside)	WP	(Mahato, Sahu et al. 1991)
35	Anagalligenin B-3-{β-D-glucopyranosyl (1 → 2)-[β-D-glucopyranosyl (1 ar 4)]-α-L-arabinopyranoside}	WP	(Mahato, Sahu et al. 1991)
36	Anagallosides A	WP	(Abdel-Gawad et al., 2000)
37	Anagallosides B	WP	(Abdel-Gawad et al., 2000)
38	Anagallosides C	WP	(Abdel-Gawad et al., 2000)
39	Desglucoanagalloside A	AP	(Soberón, Sgariglia et al. 2017)
40	Desglucoanagalloside B (Anagallisin C)	AP	(Soberón, Sgariglia et al. 2017)
41	Anagallosaponins I (Anagallisin A)		(Shoji et al., 1994)
42	Anagallosaponins II		(Shoji et al., 1994)
43	Anagallosaponins III		(Shoji et al., 1994)
44	Anagallosaponins IV		(Shoji et al., 1994)
45	Anagallosaponins V		(Shoji et al., 1994)
46	methyl anagallosaponin I		(Shoji et al., 1994)
47	Anagallosaponins VI		(Shoji et al., 1994)
48	Anagallosaponins VII		(Shoji et al., 1994)
49	Anagallosaponins VIII		(Shoji et al., 1994)
50	Anagallosaponins IX		(Shoji et al., 1994)
51	Apoanagallosaponins III		(Shoji et al., 1994)
52	Apoanagallosaponins IV		(Shoji et al., 1994)
53	Anagallisin B	AP	(Soberón, Sgariglia et al. 2017)
	PHYTOSTEROLS		
54	β-sitosterol	A, F	(Asolkar & Chopra, 1992, Yusuf et al., 1994)
55	Stigmasterol		(Asolkar & Chopra, 1992, Yusuf et al., 1994)

AP: aerial parts; F: flowers; WP: whole plant.

in a plant (Tungmunnithum, Thongboonyou, Pholboon, & Yangsabai, 2018; Yadav, Krishnan, & Vohora, 2019). To date, twenty (**1–20**) flavonoid derivatives have been isolated and identified from different parts of *A. arvensis*. The chemical structures of these flavonoids are given in Fig. 2. The important flavonoids which have been isolated from different parts of *A. arvensis* are kaempferol 3-glucuronide **(1)**, kaempferol 7-glucoside **(2)**, kaempferol 3-glucuronosyl glucoside **(3)**, kaempferol 3, 7-diglucoside **(4)**, quercetin 3- glucuronide **(5)**, quercetin 3- glucoside **(6)**, quercetin 7- glucoside **(7)**, quercetin 3-glucuronosyl glucoside **(8)**, quercetin 3-glucuronide 3-glucoside

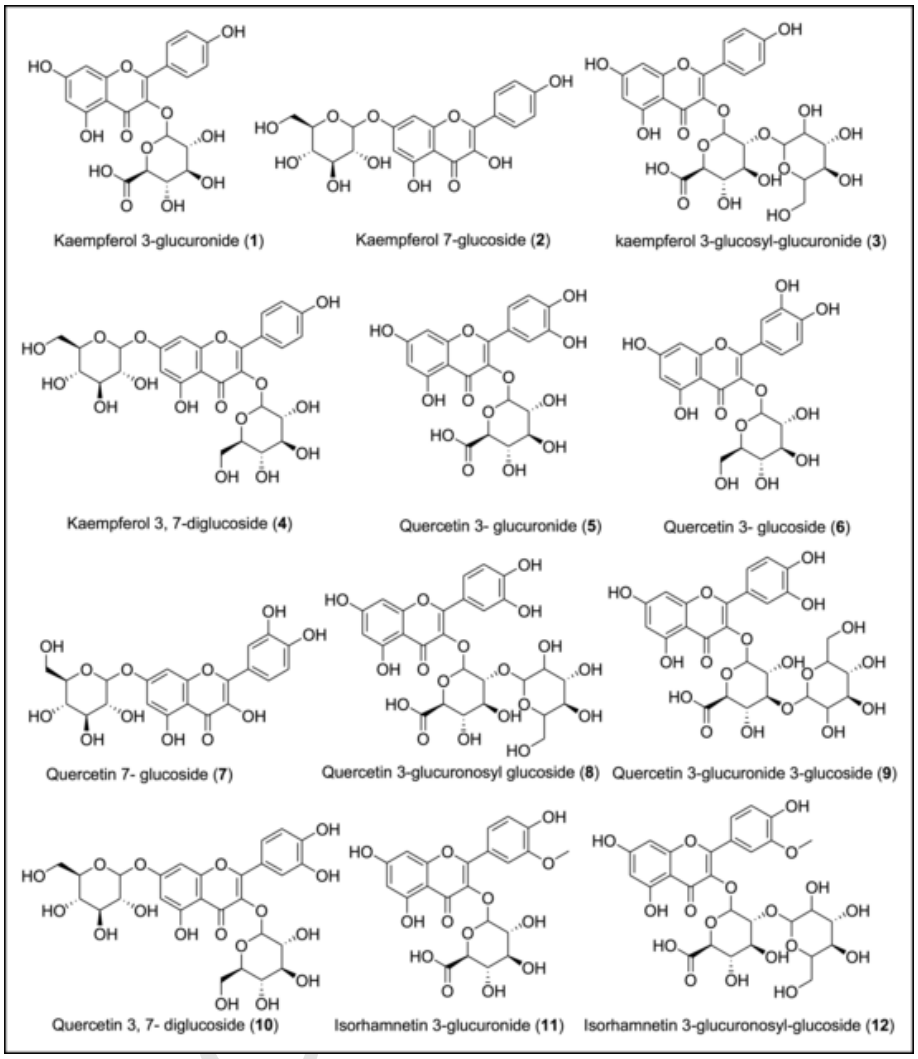

Fig. 2a. Flavone and flavone glycosides reported from *A. arvensis*.

(9), quercetin 3, 7- diglucoside **(10),** isorhamnetin 3-glucuronide **(11),** isorhamnetin 3-glucuronosyl-glucoside **(12),** isorhamnetin 3-galactosyl-glucoside **(13)** (Kawashty, El-Garf, & El-Negoumy, 1998).

Glycosides of kaempferol (**1**–**4**) were known for their wide range of biological effects, including anticancer, antioxidant, antimicrobial, anti-inflammatory, cardioprotective, antidiabetic, neuroprotective, anti-osteoporotic, antiestrogenic, antiallergic, anxiolytic, and analgesic activities (M Calderon-Montano, Burgos-Morón et al. 2011). Similarly glycosides of quercetin (**5**–**10**) which constitutes the major portion of the secondary metabolites isolated from this plant possess a board range of pharmacological properties; anti-inflammatory, antihypertensive, vasodilatory, antiobesity, antihypercholesterolemic, and antiatherosclerotic activities (Sultana & Anwar, 2008, Salvamani, Gunasekaran, Shaharuddin, Ahmad, & Shukor, 2014). It was suggested that glucuronide derivatives of quercetin are absorbed and circulated throughout the body, where it may exert beneficial functions in target tissues (Kawabata, Mukai, & Ishisaka, 2015). Likewise, another flavonoid derivative class named anthocyanins are water-soluble plant pigments belonging to the major class of secondary metabolites flavonoids and are synthesized *via* the phenylpropanoid pathway. They are present in almost all the tissues of higher plants, including leaves, fruit, stem, root, and flowers (Kendall, 2012). Three anthocyanins named malvidin 3- rhamnoside **(14)** (Giannasi, 1988; Ishikura, 1981), malvidin 3- glucoside **(15)** and pelargonidin **(16)** (Harborne, 1968, Kawashty et al., 1998) have been reported to be present in different parts of *A. arvensis*. Similarly, the petal extracts of *A. arvenis* was found to contain four important flavonoids as luteolin **(17),** luteolin 7-glucoside **(18),** quercetin 3-rhamnoside **(19)** (Ishikura, 1981) and rutin **(20)** (Asolkar & Chopra, 1992, Yusuf, Chowdhury, Wahab, & Begum, 1994).

2.4.2. Triterpenoids

Triterpenoids are widely distributed in both edible and ethnomedicinal plants; they can also be found in any animals and marine organisms. These compounds are structurally diverse, and they are characterized by a backbone of 30 Carbon modified in multiple ways that enable a formation of more than 20,000 members (Rascon-Valenzuela, Velazquez-Contreras, Garibay-Escobar, & Robles-Zepeda, 2017). Triterpenoids are one of the main active and abundant ingredients in *A. arvensis*. As presented in Table 4 and Fig. 3, thirty-three triterpenoid derivatives (**21**–**53**) have been isolated and identified from this plant. *A. arvensis* aerial parts have been reported for the isolation of triterpenoids including arvenin I (2-*O*-β-D-glucopyranosyl Cucurbitacin B **(21),** arvenin II (2-*O*-β-D-glucopyranosyl 23,24-dihydro- Cucurbitacin B **(22)** (Yamada, Hagiwara, Iguchi, & Suzuki, 1977), arvenin III (2-*O*-β-D-glucopyranosyl Cucurbitacin D **(23),** arvenin IV (2-*O*-β-D-glucopyranosyl 23,24-dihydro- Cucurbitacin R) **(24)** (Yamada et al., 1978), dihydrocucurbitacin **(25),** cucurbitacin B **(26),** cucurbitacin D **(27),** cucurbitacin E **(28),** cucurbitacin I **(29),** cucurbitacin L **(30),** and cucurbitacin Q **(31)** (Cai, Fang et al.

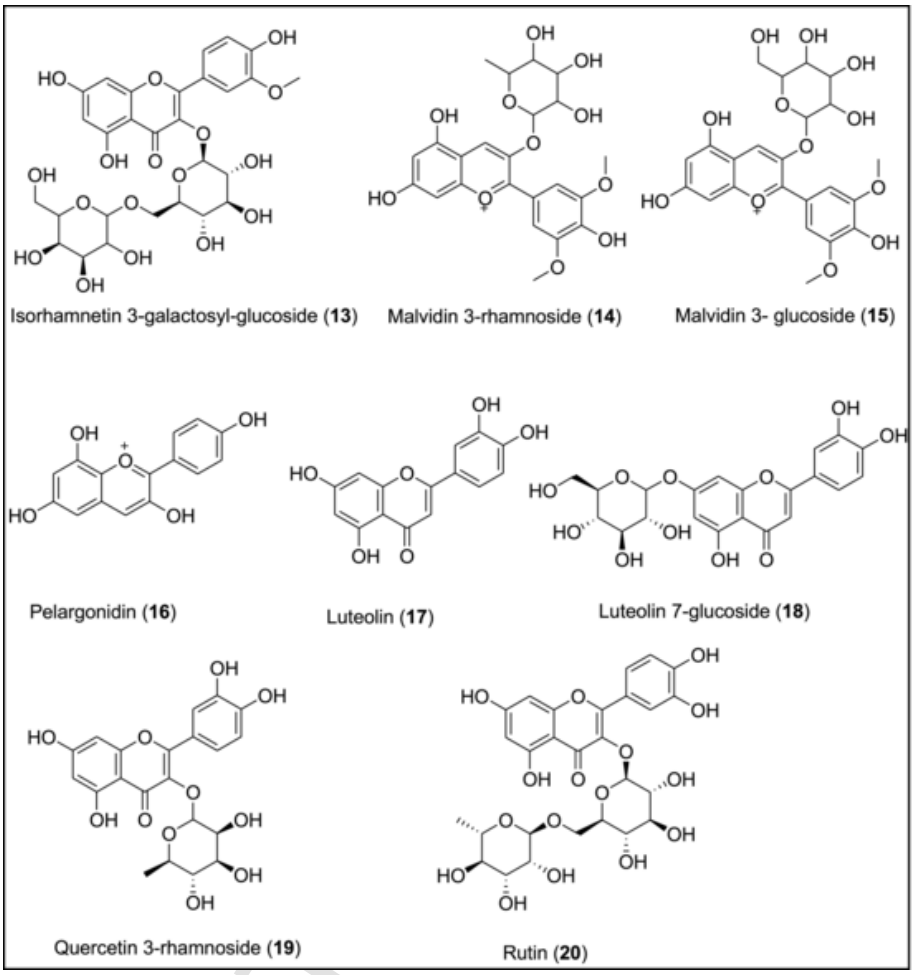

Fig. 2b. Flavone and flavone glycosides reported from *A. arvensis*.

2015). Cucurbitacins are tetracyclic triterpenes and possess a wide range of pharmacological properties, including anti-inflammatory, antipyretic and anticancer activities (Chen, Chiu, Nie, Cordell, & Qiu, 2005; Lee, Iwanski, & Thoennissen, 2010). Cucurbitacin B (**26**), D (**27**), E (**28**), I (**29**), L (**30**), and Q (**31**) have been reported for antiproliferative activities (Ahmed & Halaweish, 2014, Seo et al., 2014). Several derivatives of cucurbitacins are best known for anticancer potential, for example, cucurbitacin B (**26**) inhibits the growth of breast cancer (Gupta & Srivastava, 1773), laryngeal cancer (Liu, Peng, Zhang, Deng, & Wu, 2010), hepatocellular carcinoma (Zhang et al., 2009), melanoma (Zhang et al., 2011), lung cancer (Kausar et al., 2013), pancreatic cancer (Iwanski et al., 2010), and prostate cancer (Gao, Islam, Tian, Lui, & Xiao, 2014). Similarly, cucurbitacin I (**29**) showed the inhibitory effects on colon cancer (Kim, Park, & Kim, 2014), nasopharyngeal carcinoma (Lui et al., 2009), glioblastoma (Yuan et al., 2014), and non-small cell lung cancer (Hsu et al., 2011). Likewise, cucurbitacin E (**28**) is a potent compound to treat cancer of the bladder (Huang et al., 2012). All these derivatives are considered to be a potential candidate for future anticancer drugs. Furthermore, PC-3 xenograft mouse model is used to test the anti-prostate effect of cucurbitacin B (**26**) (Gao et al., 2014) which suppresses the growth of Panc-1 human pancreatic tumour xenografts as well (Thoennissen et al., 2009), while cucurbitacin I (**29**) promotes apoptosis in colon cancer tested by tumour models of syngeneic transplanted mice (Kim & Kim, 2015).

Similarly, Mahato et al. (1991) reported four triterpenoid oligoglycosides isolated from the aerial part of *A. arvensis*. These triterpenoids were respectively defined to be anagalligenin B 3-0-{β-D-xylopyranosyl (1 → 2) -β-D-glucopyranosyl (1 → 4)-[β-D-glucopyranosyl-(1 → 4)-β-D-glucopyranosyl(1 → 2)]-α-L-arabinopyranoside (**32**), anagalligenone 3-0-{β-D-xylopyranosyl (1ar2)-β-D-glucopyranosyl (1ar2)-β-D-glucopyranosyl(1ar4)-[β-D glucopyranosyl(1 → 2)]-α-L arabinopyranosid (**33**), anagalligenone 3-0-{β-D-xylopyranosyl (1 ar 2)-α-D-glucopyranosyl (a ar 4)-[β-D-glucopyranosyl-(1ar2)]-α-L-arabinopyranoside) (**34**), and anagalligenin B-3-0-{β-D-glucopyranosyl (1 → 2)-[β-D-glucopyranosyl (1 ar 4)]-α-L-arabinopyranoside**}** (**35**) (Mahato, Sahu et al. 1991).

Likewise, five triterpene saponins, named anagalloside A (**36**), anagalloside B (**37**), anagalloside C (**38**), desglucoanagalloside A (**39**), and desglucoanagallosid B (**40**), were isolated from the herb of *A. arvenis* (Glombitza & Kurth, 1987, Abdel-Gawad et al., 2000; Soberón, Sgariglia et al. 2017). Theses triterpene s ap onins are important secondary metabolites, and anagalloside B acts as a main precursor to inhibit the LPS-induced IL-8 and TNF-α mRNA level expressions (Dall'Acqua et al., 2010).

From the herb of *A. arvensis*, novel oleanane glycosides, anagallosaponins I–V (**41**–**45**), an artefact methyl anagallosaponin I (**46**), along with previously reported anagalloside A (**36**), anagalloside B (**37**), anagalloside C (**38**), desglucoanagalloside A (**39**,) and desglucoanagallosid B (**40**) (Shoji, Umeyama, Yoshikawa, & Arihara, 1994). Furthermore four more oleanane glycosides; anagallosaponins VI (**47**) anagallosaponins VII (**48**), anagallosaponins VIII (**49**) and anagallosaponins IX (**50**) have been isolated from same plant. The structures of these oleanane glycosides were elucidated by chemical and spectral methods. Anagallosaponins VI and VII were characterized as priverogenin B 3-*O*-β-D-xylopyranosyl (1 → 2)-β-D-

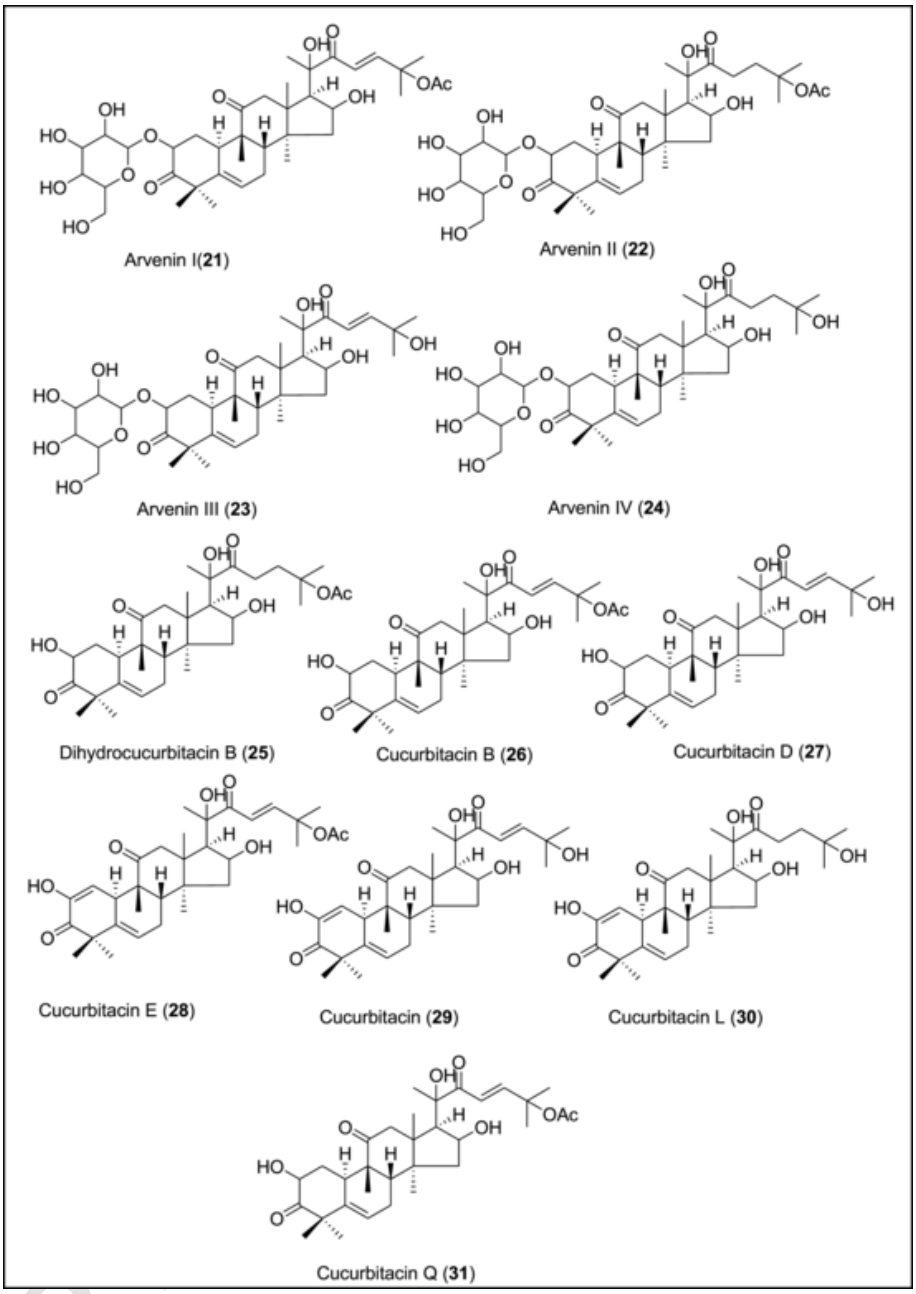

Fig. 3a. Terpenoids reported from *A. arvensis*.

glucopyranosyl (1 → 4)-β-L-arabinopyranoside and 3-*O*-{β-D-glucopyranosyl (1 → 4)-[β-D-xylopyranosyl (1 → 2)] β-D-glucopyranosyl (1 → 4)-α-L-arabinopyranoside, respectively. Whereas, the structures of anagallosaponins VIII and IX were characterized as 23-hydroxypriverogenin B 22-acetate 3-*O*-{β-D-xylopyranosyl (1 → 2)-*O*-β-D-glucopyranosyl (1 → 4)[β-D-glucopyranosyl (1 → 2)]-a-L-arabinopyranoside}, 3-*O*-{β-D-glucopyranosyl (1 → 4)-[β-D-xylopyranosyl (1 → 2)]β-D-glucopyranosyl (1 → 4)[β-D-glucopyranosyl (1 → 2)]-α-L-arabinopyranoside}, respectively. The structures of apoanagallosaponins III and IV were characterized as camelliagenin A 16-acetate 3-*O*-β-D-xylopyranosyl (1 → 2)-β-D-glucopyranosyl (1 → 4)-α-L-arabnopyranoside, 3-*O*-{β-D-xylopyranosyl (1 → 2)-*O*-β-D-glucopyranosyl (1 → 4)[β-D-glucopyranosyl (1 → 2)]-α-L-arabinopyranoside}, respectively. Along with these oleanane glycosides, the two artefact compounds anagallosaponins III (**51**), and IV (**52**) were also reported from this plant. (Shoji, Umeyama, Yoshikawa, & Arihara, 1994).

Soberón et al. (2017), reported the isolation of previously reported compounds; anagallisin C (desglucoanagallosideB) (**40**), anagallisin A (anagallosaponin I) (**47**), anagallisin B (**53**), and desglucoanagalloside A (**39**) and evaluated them for their antifungal potential (Soberon et al., 2017).

2.4.3. Phytosterols

Phytosterols are phytosteroids which include plant sterols and stanols. They have a resemblance to cholesterol, with only one variation in the carbon side chain and/or presence or absence of a double bond (Abumweis, Barake, & Jones, 2008). Two phytosterols as also indicated in Table 4, namely β-sitosterol **(54)** and stigmasterol **(55)** (Asolkar & Chopra, 1992, Yusuf et al., 1994) have been isolated from

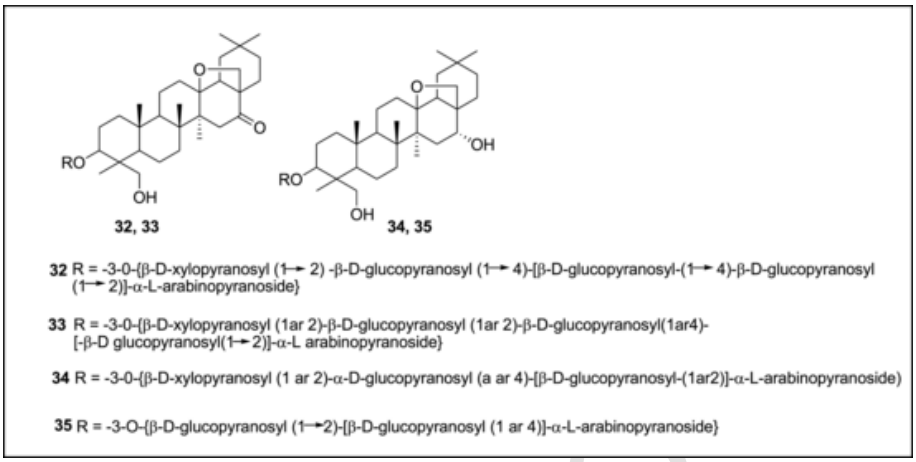

Fig. 3b. Terpenoids reported from *A. arvensis*.

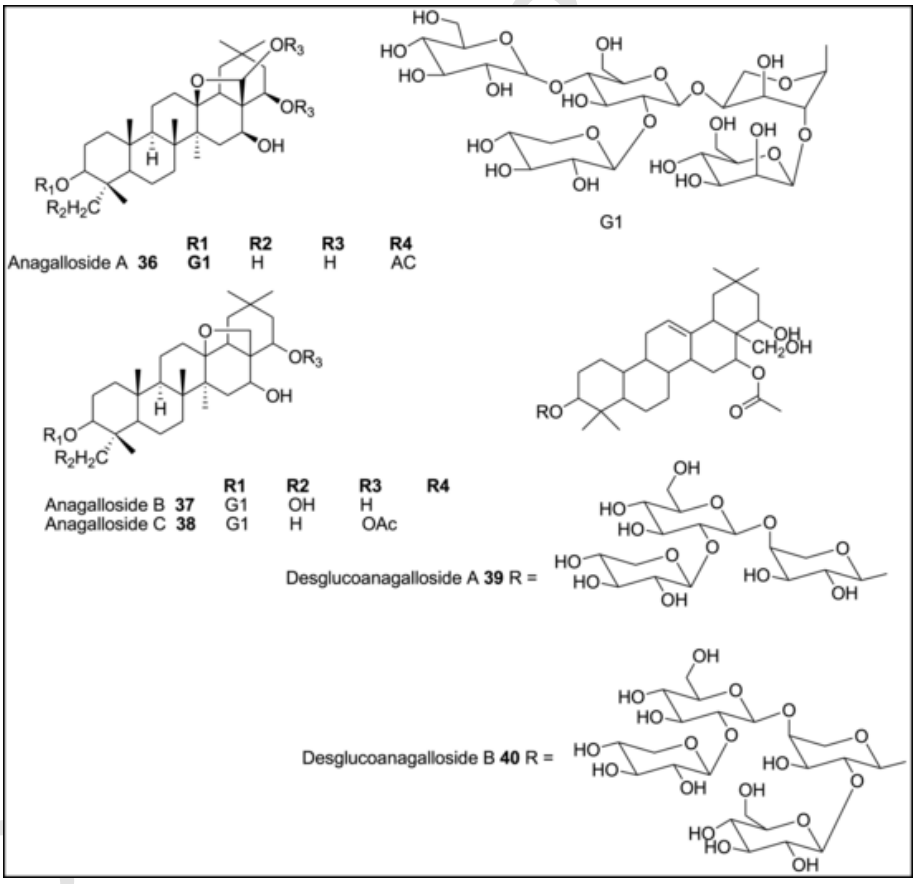

Fig. 3c. Terpenoids reported from *A. arvensis*.

A. arvensis. The chemical structures of the phytosterols isolated from *A. arvensis* are shown in Fig. 4.

2.5. Preliminary phytochemical screening

Preliminary phytochemical screening of methanol extract of *A. arvensis* led to the presence of saponins, glycoside, flavonoids, tannins, alkaloids, resin and phenols (López et al., 2013) which are know bioactive compounds. Another research work conducted for the phytochemical testing of *A. arvensis* leaves methanol extract led to the presence of glycosides, saponins, amino acids, terpenes, and alkaloids. At the same time, tannins were found to be not present (Khoshkholgh-Pahlaviani, Massiha et al., 2013). Similarly, the different extracts (aqueous, aqueous-ethanol, ethanol, chloroform, and petroleum ether) of fresh *A. arvensis* plant during the flowering period was tested for the presence of various secondary metabolites classes. The results indicated that all the extracts contained proteins, while chloroform extract contained flavonoids as well as proteins (Attard & Pacioni, 2012). Likewise, *A. arvensis* seeds have been reported to contain anthraquinones, flavonoids, saponins, alkaloids, glycosides, steroids, and tannins. The amounts of alkaloids, saponins, flavonoids and tannins were 2.21, 1.29, 4.43, and 9.56%, respectively (Abbas et al., 2012; Al-Snafi, 2015).

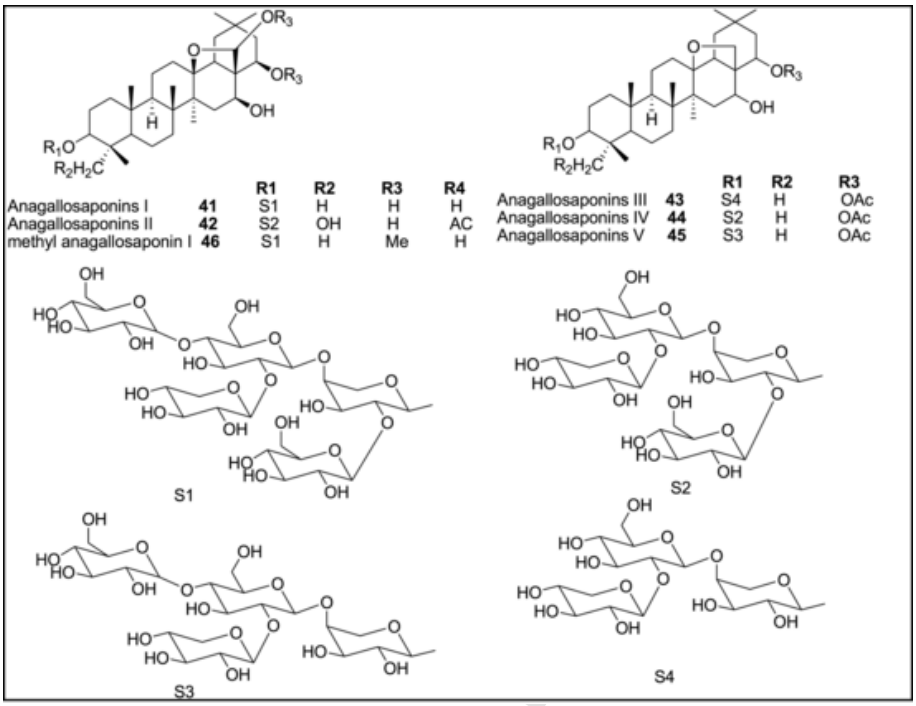

Fig. 3d. Terpenoids reported from *A. arvensis*.

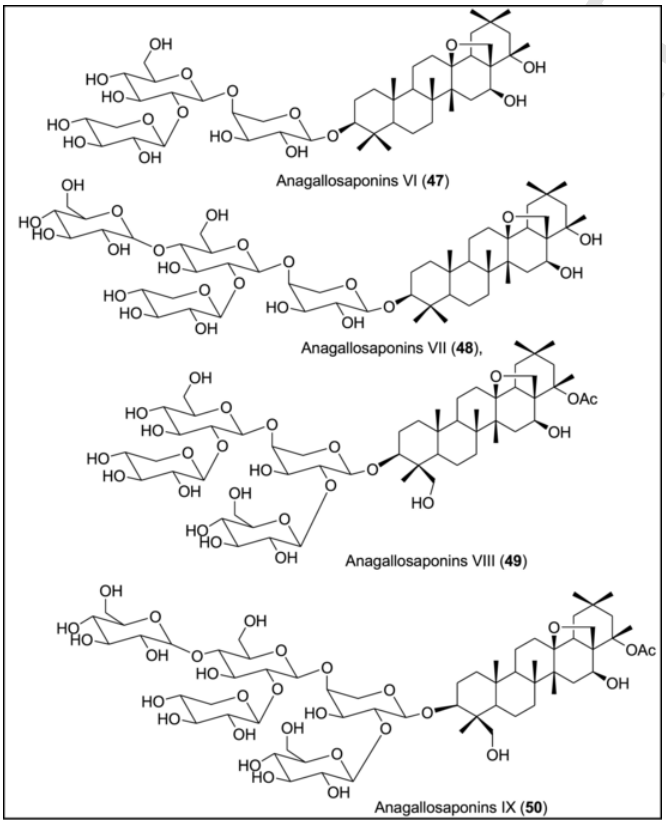

Fig. 3e. Terpenoids reported from *A. arvensis*.

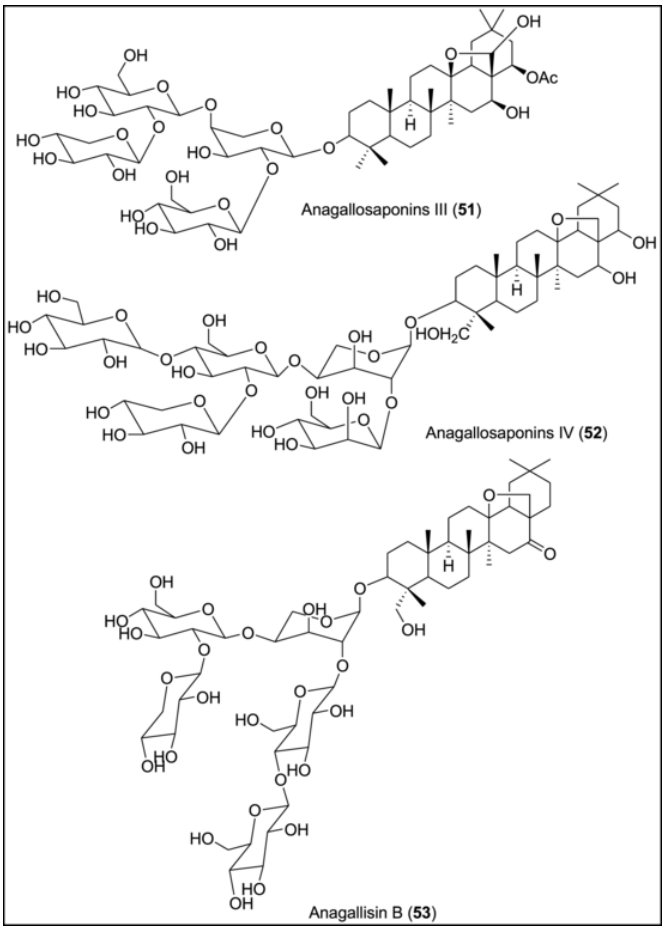

Fig. 3f. Terpenoids reported from *A. arvensis*.

2.6. Pharmacological activities

On account of claimed wide-ranging pharmacological effects, *A. arvenis* has been employed for many healing benefits. Although, the scientific studies have supported only a few of its activities yet. Most

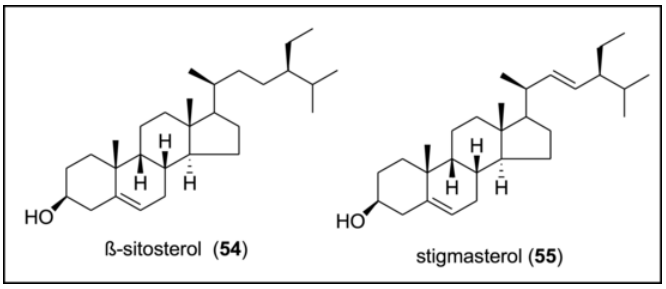

Fig. 4. Phytosterols reported from *A. arvensis*.

of the reported pharmacological activity-based studies are conducted to explore the antibacterial and antifungal potential of *A. arvensis,* and these have been listed in Table 5. While, fewer research groups have tested this plant species for other biological effects (Table 6) including antioxidant, anti-leishmanial, molluscicidal, anti-inflammatory, anticancer, analgesic, etc. Most of these above mentioned pharmacological studies were crude extract-based, however, some of the researchers, as presented in Table 7, have also reported the anti-viral, antifungal, molluscicidal, genotoxicity, toxicity, and antifertility activities on the isolated compounds from different parts of *A. arvensis*. The details of various pharmacological activities as having been reported from *A. arvensis* is discussed below:

2.6.1. Antibacterial activity

Nowadays, the misuse of antibiotics has been considered a serious concern worldwide, which ultimately headed towards adverse consequences including the occurrence of multiple-resistant bacteria with nosocomial infections and increased medical cost (Liu, Peng, Zhang, Deng, & Wu, 2010). Henceforth, the discovery of new antibacterial agents or other alternative therapeutic approaches is demanding. The antibacterial activity of methanol and aqueous extracts of *A. arvenis* aerial parts were probed by employing a microplate dilution method against four bacteria named *Escherichia coli*, *Staphylococcus aureus*, *Bacillus subtillis*, and *Pseudomonas aeruginosa*. As a positive control drug, streptomycin was selected. The methanol extract showed significant inhibition against only two bacteria, i.e., *E. coli* (MIC; > 2.5 mg/mL) and *B. subtillis* (MIC; 1.25 mg/mL), while inactive for

Table 5
Antibacterial and antifungal activities of *A. arvensis*.

Activity	Tested substance	Model	Positive control	Microorganisms	Dose range	Results	Ref
Antibacterial	Methanol and aqueous extracts of aerial	Microplate dilution method	Streptomycin	*Bacillus subtillis*, *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*	NA	Methanol extract against *E. coli* (MIC; > 2.5 mg/mL) and *B. subtillis* (MIC; 1.25 mg/mL) Aqueous extract was inactive	(López et al., 2013)
	Ethanol and aqueous extracts of *A. arvensis* aerial parts	Disc diffusion method	Ampicillin, penicillin-G and, gentamicin	*S. aureus*, *E. coli*, *Klebsiella pneumoniae*, *Proteus vulgaris*, *P. aeruginosa*	200 mg/mL	All extracts presented moderate activity.	(Ali-Shtayeh et al., 1998)
	A. arvensis leaves methanol extract	Disc diffusion and micro-broth dilution method	Vancomycin	Clinical isolates of *multiple resistant Staphylococcus aureus* (MRSA)	50–500 µg/mL	MIC extract > 100 µg/mL MIC vancomycin 14.5 µg/mL	(Sharifi-Rad et al., 2016)
Antifungal	Aqueous extract of *A. arvensis*	Agar dilution method	Griseofulvin	*Microsporum canis*, *Trichophyton mentagrophytes* and *Trichophyton Violaceum*.	0.01–3 mg/mL	MIC values for *M. canis*: 16, *T. mentagrophytes*: 25, and *T. violaceum*: 15 ug/mL	Ali-Shtayeh and Abu Ghdeib (1999)Ali-Shtayeh and Abu Ghdeib (1999)
	DCM, EA, and methanol extracts of aerial parts of *A. arvensis*	Mycelial growth method	Benzoic acid Gallic acid	*Rhizopus stolonifera*	250–1000 ppm	MIC value for methanol:1000 ug/mL MIC value of EA: 500 ug/mL DCM extract: 10% growth inhibition Aq extract: no inhibition	(Lopez, Akerreta et al., 2008)
	Methanolic extract of the whole plant	Agar diffusion method	1 mL 50% methanol	*Phytophthora drechsleri*, *Pythium aphanidermatum* and *Rhizoctonia solani*.	2000 ppm	% inhibiton for *P. drechsleri:* 48.60, *P. aphanidermatum:* 11.05, and *R. solani:* 40.74	(Bahraminejad et al., 2013)
	Methanol and water extract of the whole plant	Paper disc method	Mancozeb, Carboxin Thiram, and Benomyl	*Fusarium oxysporum*, *Rhizoctonia solani*, *Cochliobolus sativus*	5 mg/disc	The methanol extract was found more active.	(Bahraminejad et al., 2011)
	Ethanol, petroleum ether and aqueous extracts of *A. arvensis*	Agar diffusion technique	Dithane	*Rhizopus* spp, *Mucor* spp, and *Aspergillus flavus*	NA	The ethanol extract was most active with MIC of 120 mg/well (*Rhizopus* spp), 120 mg/well (*Mucor* spp), and 90 mg/well (*Aspergillus flavus*)	(Cortez-Rodríguez et al., 2014)
	A. arvensis methanol and aqueous extract	Broth microdilution assay	Amphotericin B	*Candida albicans*	NA	Methanol extract MIC: 0.31 mg/mL the aqueous extract was not active	(López et al., 2013)
	A. arvensis leaves methanol extract	Agar disc diffusion	Nystatin	*Candida albicans*	0.005–20 mg/mL	MIC: 0.25 ug/mL against the standard and clinical strain of tested fungi	(Khoshkholgh-Pahlaviani, Massiha et al., 2013)
	Ethanol and aqueous extracts of *A. arvensis* aerial parts	Disc diffusion method	Nystatin	*Candida albicans*	200 mg/mL	Ethanol extract ZOI: 8.9 mm Aqueous extract ZOI: 17.2 mm	(Ali-Shtayeh et al., 1998)

Table 6
Summary of the pharmacological activities of *A. arvensis*.

Pharmacological activity	Tested substance	Model used	Standards/ Control	Tested dose	Results	Ref.
Antioxidant	Methanol and aqueous aerial extracts	Xanthine oxidase radical scavenging activity	Caffeic acid	10-100 ug/mL	• Aq extract IC_{50}: 10.7 ug/mL. • Methanol extract IC_{50}: 20.5 ug/mL.	(López et al., 2013)
	DCM, ethyl acetate, Methanol, and aqueous aerial extracts	DPPH free radical scavenging activity	Ascorbic acid and BHT	2000-2 ug/mL	• Methanol extract IC_{50}: 113.39 μg/mL • Aqueous extract IC_{50}: 64.76 μg/mL • DCM and EA were inactive	(Lopez, Akerreta et al., 2008)
Analgesic	*A. arvensis* whole plant homoeopathic preparations	Hot plate, ice plate, Randall-Selitto, rotarod and open field assay	Normal saline	0.5 mL/ rat/day	• Increased latency time • Increases quantum of threshold pressure • Depress motor coordination and locomotor activity	(Sundaram et al., 2010)
Anticancer	Methanol and aqueous extracts of *A. arvensis* aerial parts	MTT and LDH assays PC12 and DHD/K12PROb cell lines	Triton X-100 (5%)	20-80 ug/ mL of each extract	• Both extracts reduced cell survival and induced cell damage. • PC12 cells being more sensitive to the extracts. • The methanol extract was significantly more cytotoxic.	(López et al., 2013)
Anti-inflammatory	Methanol and aqueous extracts	COX-I and COX-II inhibition assay	Indomethacin Nimesulide	0–1 mg/ mL	• The methanol extract showed significant COX inhibition • Methanol extract reduced prostaglandin synthesis • The aqueous extract was moderately active	(López et al., 2013)
Molluscicidal	The aqueous solution of *A. arvensis*	*Biomphalaria alexandrina* snails			• Reduce the survival rate of snail	Mostafa and Tantawy (2000)
	Aqueous extracts of AA leaves	*Biomphalaria alexandrina* snails	Chlorinated water	10–50 mg/ L	• LC_{50}: 37.9 mg/L • LC_{90}: 48.3 mg/L	Ibrahim and Ghoname (2018)
Anti-leishmanial	The methanol extract of the whole plant	*In vitro* intracellular amastigote assay against *L. infantum* and MDC-5_{sv2} cells	Miltefosine and amphotericin B	64–0.125 ug/mL	• Effective for anti-leishmanial activity against *L. infantum* and MDC-5_{sv2} with IC_{50} < 0.125 and 16 ug/mL, respectively	Vermeersch, Foubert et al. (2009)

Table 7
Activities of specific isolated compounds from *A. arvensis*.

Compounds	Effects	*In vitro* test	Ref.
3-*O*-glucose-(1 → 3 or 4)-[arabinose (1 → 4 or 3)]-glucose (1 → 2)-xyloside of 23-hydroxyprotoprimulagenin A	Anti-viral	• Significant inhibition for herpes simplex type 1 and poliovirus type 2 • Inhibition of virus-induced cytopathogenicity and reduction of virus yield	(Amoros et al., 1987)
3-*O*-glucose-(1 → 3 or 4)-[arabinose (1 → 4 or 3)]-glucose (1 → 2)-xyloside of 23-hydroxyprotoprimulagenin A	Anti-viral	• The saponin ointment was effective for herpetic keratitis induced in rabbit eyes	(Amoros et al., 1988)
Anagallisin C, anagallisin A, anagallisin B, and desglucoanagalloside A	Antifungal	• All the compounds were active against *C. albicans* strains. • Anagallisin C was significantly more active among all.	(Soberón, Sgariglia et al. 2017)
Desglucoanagalloside B and anagalloside B	Molluscicidal	• Strong molluscicidal effects comparable to standard nicolsamide.	(Abdel-Gawad et al., 2000)
Desglucoanagalloside, anagallosaponin, anagallisin B, and desglucoanagalloside A	Genotoxicity	• No genotoxicity was noted up to 10 ug/mL	(Soberón, Sgariglia et al. 2017)
Desglucoanagalloside, anagallosaponin, anagallisin B, and desglucoanagalloside A	Toxicity	• All compounds caused 100% haemolysis at a dose of ≥15 μg/mL • Desglucoanagalloside was found to be the most active	(Soberón, Sgariglia et al. 2017)
Anagalligenone	Antifertility	• Instantaneous immobilization of spermatozoa in 1 min	(Mohamed, Ibrahim et al., Kamboj & Dhawan, 1982)

others. The aqueous extract was inactive against all the tested bacteria (López et al., 2013). In another study, ethanol and aqueous extracts of *A. arvensis* aerial parts were tested against *S. aureus*, *E. coli*, *Klebsiella pneumoniae*, *Proteus vulgaris*, and *P. aeruginosa*, and three other strains of each of these species. Both extracts show the zone of inhibition (ZOI) of 6 mm for all tested bacteria except for *P. vulgaris* for which ethanol extract showed ZOI of 13 mm and water extract showed ZOI of 12.6 mm (Ali-Shtayeh, Yaghmour, Faidi, Salem, & Al-Nuri, 1998). Similarly, Javad et al. (2016), investigated the antimicrobial activity of methanol extract of *A. arvensis* leaves against clinical isolates of *multiple resistant Staphylococcus aureus* (MRSA) by both disc diffusion method and micro-broth dilution method. *A. arvensis* leaf methanol extract recorded different degrees of antibacterial activity on MRSA as evidenced by the inhibited zones at concentrations of 250, 300, 400 and 500 μg/mL (1.3, 1.5, 2.2 and, 2.3 mm, respectively) as per disc diffusion method. Inhibition zones of MRSA showed no significant different among extract concentrations of 50,100,150 and 200 μg/mL (P <0.05). The MICs of the plant extract and vancomycin were >100 and 14.5 μg/mL, respectively (Sharifi-Rad et al., 2016).

2.6.2. Antifungal activity

The increasing incidence and ubiquity of mycoses have become a serious public health problem as per the latest epidemiological data. Resistance has been developed due to over usage of antifungal drugs. The availability of a limited number of drugs and the spread of multidrug-resistant strains of fungus has led to the need for discovery of novel antifungals from medicinal plants (Aqil et al., 2010). The aqueous extract of *A. arvensis* was probed for its antifungal activity (using agar dilution method) against *Microsporum canis*, *Trichophyton mentagrophytes* and *Trichophyton violaceum*. The tested extract (0.01–3 mg/mL) showed the mean of percentage mycelial inhibition of tinea capitis dermatophytes against these three tested fungal strains by 94.1, 78.3 and 100%, with MIC values of 16, 25 and 15 ug/mL, respectively as compared with the reference antibiotic griseofulvin which shows MIC value of 0.6, 2.5 and 0.6 ug/mL, respectively (Ali-Shtayeh & Abu Ghdeib, 1999). Lopez et al. (2008), evaluated the antifungal activity of dichloromethane (DCM), ethyl acetate (EA), methanol and aqueous extracts of aerial parts of *A. arvensis* against *Rhizopus stolonifera*. Mycelial growth method was used to test the activity. The outcomes exhibited methanol, and EA extracts with MIC value of 1000 and 500 ug/mL, respectively Similarly, the DCM extract was least active (10% growth inhibition), while the aqueous extract did not present inhibition effects (Lopez, Akerreta et al., 2008). Another study has presented the antifungal potential of methanol extract of *A. arvensis* whole plant against three important phytopathogenic fungi including *Pythium aphanidermatum, Phytophthora drechsleri* and *Rhizoctonia solani*. Agar diffusion method was employed using 1 mL of 50% methanol as control, and the percentage inhibition of fungal growth was determined. The plant extract was found to exhibit broad-spectrum activity against the tested fungi with values of 11.05, 48.60, and 40.74% for *P. aphanidermatum, P. drechsleri* and *R. solani*, respectively (Bahraminejad, Amiri, Ghasemi, & Fathi, 2013). The methanol and water extracts of *A. arvensis* whole plant (5 mg/disc) was tested for paper disc fungal bioassay against three fungal pathogens, *Fusarium oxysporum*, *Rhizoctonia solani* and *Cochliobolus sativus* and the methanol extract was found to be most active with percentage inhibition of 9.3, 9.03 and 9.61, respectively. On the contrary, the water extract presented weak inhibition. Mancozeb, carboxin thiram and benomyl were employed as positive controls against *C. sativus*, *R. solani* and *F. oxysporum*, respectively (Bahraminejad, Abbasi, & Fazlali, 2011). Similarly, *A. arvensis* leaves extracts caused complete growth inhibition of several fungi (liquid culture technique method was used) including *Colletotrichum papaya*, *Alternaria solani*, *Glomerella cingulata*, *Helminthosporium turcicum*, *Pythium aphanidermatum* and *Rhizopus nigricans* except *Aspergillus niger*. Apart from leaf extract, the complete growth inhibition against *Colletotrichum papaya* was also reported with stem, root and flower extracts of this plant (Nene & Thapliyal, 1965). The antifungal potential of ethanol, petroleum ether and aqueous extracts of *A. arvensis* was tested against phytopathogenic fungal strains including *Rhizopus* spp, *Mucor* spp, and *Aspergillus flavus*. Agar diffusion method was employed to accomplish the activity by determining the ZOI and MIC values and comparing with the positive control dithane. The ethanol extract was found to be most active (Cortez-Rodríguez, Perales-Lara, Meneses-Sánchez, Pérez-Xochipa, & Cabrera-Hilerio, 2014). Another study has reported the antifungal activity of four isolated triterpenoid saponins (anagallisin C, anagallisin A, anagallisin B, and desglucoanagalloside A) from the aerial parts of *A. arvensis*. The activity was performed against two *Candida albicans strains*; one reference strain from ATCC (ATCC 10231), and the other was *C. albicans* 12–99 clinical isolate strain highly resistant to fluconazole (FLU). The antifungal assay was evaluated using Disk diffusion assay, Broth microdilution and cell viability assays, Checkerboard assays, Fungicidal activity assays, and antifungal activity on *C. albicans* biofilm. Among the tested compounds, anagallisin C displayed highest activity against *C. albicans* (ATCC 10231) with MIC-0 = 1 μg/mL. Likewise, the same compound presented maximum inhibitory activity against *C. albicans* ATCC 10231 sessile cells (MIC_{50}; 0.5 μg/mL and MIC_{80}; 1 μg/mL) and against C. albicans 12–99 sessile cells (MIC_{50}; 0.75 μg/mL and MIC_{80}; 1.25 μg/mL). Moreover, anagallisin C, in combination with FLU was also fungicidal for both the tested strains (Soberón, Sgariglia et al. 2017). Lopez et al. (2011) have reported the antifungal potential (broth microdilution assay) of methanol and aqueous extracts of *A. arvensis* against *Candida albicans*. Amphotericin B was used as positive control. The methanolic extract was found to be possess antifungal potential with MIC value of 0.31 mg/mL while aqueous extract was not active (López et al., 2013). In another study, the antifungal activity (against three strains of *Candida albicans*) of methanol extract (0.005–20 mg/mL) of *A. arvensis* leaves was done using the agar disc diffusion method. Nystatin was used as standard. The tested extract was found to be active with MIC value of 0.25 ug/mL against both standard and clinical isolate strain (Khoshkholgh-Pahlaviani, Massiha et al., 2013). In another study, ethanol and aqueous extracts of *A. arvensis* aerial parts were tested against *Candida albicans* and three other strains of each of this species. Both ethanol and aqueous extracts presented ZOI of 8.9 and 17.2 mm, respectively (Ali-Shtayeh et al., 1998). Another study reported *A. arvensis* ethanolic extract to have antifungal activity against phytopathogenic fungus of particular genera including *Ceratocystis, Cytospora, Fomes*, and *Pestaiotiopsis* (Abraham, Amoros, & Girre, 1983; Aliotta et al., 1992). The investigation of *A. arvensis* shoot aqueous extract was done against two epidemic fungi named *Helminthosporium sativum* and *Fusarium oxysporum*. Significant growth inhibition noted for *H. sativum* while less effects were seen against *F. oxysporum* with the shoot and root extracts of *A. arvensis*. The study indicated the potential of this plant in developing fungitoxic natural chemicals to control these troublesome plant pathogens (Qasem, 2011).

2.6.3. Antiviral activity

The antiviral activity of a triterpene saponin (2.5–10 ug/mL) named 3-*O*-glucose (1 → 1→3 or 4)– [arabinose (1 → 1→ 4 or 3)] –glucose (1 → 2)-xyloside of 23- hydroxyprotoprimulagenin A purified from *A. arvensis* was probed for antiviral potential against viruses including adenovirus type 6, vesicular stomatitis, herpes simplex type 1, poliovirus and vaccinia. The replication of poliovirus type 2 and herpes simplex virus type 1 was inhibited by the compound as mentioned above as by inhibition of cytopathic effect and reduction of virus production. The observed anti-viral effects were primarily due to the inhibition of cell attachment to virus-host (Amoros, Fauconnier, & Girre, 1987). Another study has presented the antiviral (against Herpes Simplex Keratitis in Rabbits) activity of the ointment prepared from the mixture of two saponins (major saponin was identified as the 3-*O*- glucosyl(1 → 3 or 4)-(arabinosyl (i→4 or 3)-glucosyl(1 → 2)-xyloside of 23-hydroxyprotoprimulagenin A) which were isolated from *A. arvensis* whole plant. Standard antiviral drugs, idoxuridine, adenine arabinoside, and acycloguanosine were employed as a positive control. The saponin ointment appeared to be as effective as adenine arabinoside, and from days 10–14 post-inoculation was better than idoxuridine (Amoros, Fauconnier, & Girre, 1988).

2.6.4. Molluscicidal activity

Schistosomiasis is one of the significant public health concerns, that affects about 200 million people around the globe, caused by the infestation of the host by Schistosoma species (Lockyer et al., 2003; Han et al., 2010). A study conducted by Mahfouz et al. (2000), has reported the strong molluscicidal effects of two isolated saponins (desglucoanagalloside B and anagalloside B) against the schistosomal intermediate hosts, i.e., *Biomphalaria glabrata* and *Oncomelania*

quadrasi. Niclosamide was used as a standard in this study (Abdel-Gawad et al., 2000). Similarly, in another study, the aqueous solution of *A. arvensis* reduced the survival of *B. alexandrina* snails with time (Mostafa & Tantawy, 2000). Another report has evaluated the molluscicidal potential of aqueous extracts (10–50 mg/L) of *A. arvensis* leaves against *Biomphalaria alexandrina* snails. The plant extract was found to be active against the tested snail with LC_{50} and LC_{90} values of 37.9 mg/L and 48.3 mg/L, respectively (Ibrahim & Ghoname, 2018).

2.6.5. Antioxidant activity

Due to the toxicity profile of synthetic drugs, the antioxidants from plants are preferred and presumed to be safer. Antioxidants terminate free radical-mediated oxidative reactions that ultimately play an essential role in protecting the body against certain diseases (Havsteen, 2002). A study conducted by Lopez et al. (2011) has reported the xanthine oxidase free radical scavenging antioxidant potential of methanol and aqueous extracts of *A. arvensis* aerial parts. Caffeic acid was used as standard. Both the extracts exerted dose-dependent antioxidant effects with IC_{50} values of 20.5 and 10.7 ug/mL for methanol and aqueous extract, respectively. Moreover, both the extracts were also evaluated for xanthine oxidase inhibition potential and were found inactive (López et al., 2013). Similarly, another study has reported the DPPH free radical antioxidant activity of different polarity (DCM, EA, methanol, and aqueous) extracts (2000–2 ug/mL) of *A. arvensis* aerial parts. Methanol and aqueous extracts presented considerable antioxidant effects with IC_{50} values of 113.39 and 64.76 μg/mL, respectively while the DCM and ethyl acetate extracts were inactive. Ascorbic acid and 2,6-di-tert-butyl4-hydroxytoluene (BHT) were used as positive controls (Lopez, Akerreta et al., 2008). As the pharmacological relevance of chemical-based antioxidant assays such as DPPH method has not been proven; therefore, both *in vitro* and *in vivo* animal models must be employed to demonstrate the antioxidant activity of plant to consider it relevant (Harnly, 2017, Ashokkumar, Murugan, Dhanya, & Warkentin, 2019).

2.6.6. Analgesic/behavioural effects

The effects of different strengths (3x, 6x, 12x and 30 C) of homoeopathic drug preparation of *A. arvensis* whole plant administered at a daily dose of 0.5 mL/rat/day was assessed and screened for analgesic effect (hot plate, ice plate and Randall-Selitto methods) and behavioural activities (rotarod and open field assay). The thermal sensation on the hot plate while cold sensation on ice plate methods was investigated for all of the four different strengths of *A. arvensis* with a resultant increase in latency time. The mechanical induction of pain in Randall-Selitto assay showed an increase in threshold pressure and a decrease in locomotor activity and motor coordination. The maximum analgesic and behavioural effects were seen on the 10^{th} day, but by 20^{th} and 30^{th} day, the effects were radically reduced. The overall results suggest that this plant possess central nervous system depression potency (Sundaram et al., 2010). The major limitation of this study is the absence of any positive control drugs. Further studies employing some more analgesic models and comparisons with the standard controls are recommended.

2.6.7. Anticancer/cytotoxic activity

The principal cause of death in cancer treatment is due to the development of resistance to drug therapy (Batist et al., 2011). Specific mechanisms take part in developing resistance that includes a change in cellular pathways, reduction in uptake and increase in efflux of a drug (Cornejo-García et al., 2016). The progeny of resistance related to synthetic anticancer drugs can be overcome by plant molecules, and for that purpose, about 3000 plants have yet been investigated for anticancer potential (Solowey et al., 2014) including *A. arvensis*. The cytotoxic activity (employing 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) and lactate dehydrogenase (LDH) assays) of methanol and aqueous extracts from *A. arvensis* aerial parts were assessed against PC12 (neuroblastic cell line) and DHD/K12PROb (colonic adenocarcinoma cell line) cells. Triton X-100 (5%) was used as a control substance to induce cell death. Both the extracts were tested at the dose ranging from 20 to 80 ug/mL of each extract and found to induce cell damage (LDH release) and reduced the cell survival. PC12 cells were noted to be more sensitive to the extracts than DHD/K12PROb cells. Overall, methanol extract was found to be more cytotoxic (López et al., 2013). Another research work has reported the four triterpenoid saponins (desglucoanagalloside, anagallosaponin, anagallisin B, and desglucoanagalloside A) isolated from aerial portions of *A. arvensis* were tested (1–200 μg/mL) for human red blood cell toxicity by quantification of hemolytic effect. Triton X-100 was used as a positive control drug. All the four tested compounds caused 100% haemolysis at the dose of ≥15 μg/mL. Desglucoanagalloside was found to be the most active one among all tested compounds (Soberón, Sgariglia et al. 2017). Likewise, in a review paper by Cai et al. (2015), the plant *A. arvensis* is highlighted to contain a triterpene derivative name cucurbitacin B, which is very useful for treating different types of cancers includes breast cancer, hepatocellular, prostate, laryngeal, pancreatic, lung, and melanoma. Cucurbitacin has anticancer action on glioblastoma, colon cancer, nasopharyngeal, and lung cancer (Cai, Fang et al. 2015). Overall, limited studies have probed into the anticancer potential of *A. arvensis* extracts and isolated compounds, and these are executed *in vitro*, not *in vivo*. Hence, future investigations should be focused on the cytotoxic bioactivity of *A. arvensis* in various clinical studies with animals.

2.6.8. Anti-inflammatory activity

Inflammation is a physiological process and an essential part of any host defence and tissue damage. The post-injury wound healing comprehends with three phases that include the inflammation phase followed by proliferation and maturation phase. The inflammation phase acts as a protective shield against microbial contaminations (Kondo, 2007), and the healing period is effectively minimized (Shimizu et al., 2000). Methanolic and aqueous extracts of *A. arevensis* were tested for their anti-inflammatory potential using cyclooxygenase 1 (COX-1) and COX-2 assays. Indomethacin and nimesulide were used as reference standards for COX-1 and COX-2, respectively. The methanol extract showed significant cyclooxygenase inhibition and reduced the prostaglandin synthesis; however, the aqueous extract was only moderately active (López et al., 2013).

2.6.9. Anti-leishmanial activity

The parasitic infection, i.e., leishmaniasis affects 12 million people around the globe (Takahashi, Fuchino, Satake, Agatsuma, & Sekita, 2004). Localized skin lesions, dissipated infection of viscera and mucous membrane are among the symptoms related to this disease (Murray, Berman, Davies, & Saravia, 2005; Almubayedh & Ahmad, 2019). The methanolic extract of whole *A. arvensis whole* plant was tested for the anti-leishmanial activity by employing standard *in vitro* intracellular amastigote assay with *Leishmania infantum* and MDC-5_{sv2} cells for cytotoxicity and selectivity evaluation. Miltefosine and amphotericin B were used as reference standards. The results indicated the plant extract to be much useful for anti-leishmanial activity against *Leishmania infantum* and MDC-5_{sv2} with $IC_{50} < 0.125$ and 16 ug/mL, respectively (Vermeersch, Foubert et al. 2009).

2.6.10. Genotoxic activity

The therapeutic potential of any administered drug is dependent mainly on the assessment of its safety profile. During past decade, the scientific community has started paying more interest towards natural products and their active constituents, and as per the recommendations of international regulatory agencies genotoxic profile of natural therapeutic agents should be determined (Calapai & Caputi,

2007, Tsuboy et al., 2010). Chromatographic and HPLC experiments performed with aerial parts of *A. arvensis* yielded four triterpenoid monodesmosidic saponins named as anagallisin C (also named as desglucoanagalloside B), anagallisin A (also named as anagallosaponin I), Anagallisin B and desglucoanagalloside A (also named as anagallosaponin VIII). The genotoxic response of these isolated compounds (0.03–20 μg/mL) was evaluated using *Bacillus subtilis* rec assay followed by quantification and Probit transformation of the differential growth curves of *B. subtilis* rec strains exposed to samples. The outcomes attributed to S-Probit were compared with the reference. As a genotoxic reference, potassium dichromate ($K_2Cr_2O_7$) was used while fluconazole (FLU) was employed as a non-genotoxic reference. S-Probit values and interpretations obtained through *B. subtilis* rec assay revealed that all of these four compounds and FLU were not genotoxic on *B. subtilis* rec strains ($-0.123 >$ S-Probit > 0.199). At the same time, $K_2Cr_2O_7$ displayed a significant genotoxic effect (S-Probit > 0.593) (Soberón, Sgariglia et al. 2017).

2.6.11. Hepatoprotective activity

The regulation of biochemical pathways and various pivotal functions in a body are governed by the liver (Sharma, Chakraborti et al. 1991). The toxicity of liver termed as hepatotoxicity is a severe concern that results from the consumption of alcohol, certain drugs/antibiotics, chemicals, and microbial infections. Hepatoprotective medicinal plants are the best substitute in this regard (Sharma et al., 1991; Senthilkumar, Karuvantevida, Rastrelli, Kurup, & Cheruth, 2018). *A. arvensis* herb has therapeutic value for liver ailments because of the presence of cucurbitacin (Yamada et al., 1978), a phytoconstituents responsible for liver ailments.

2.6.12. Antifertility activity

The population explosion has created a grave setback in the economic growth and all-round human development in developing countries and demands an immediate betterment of new potential contraceptives. The quest for the oral contraceptive agent that can control human fertility is as old as recorded history. Although a wide variety of synthetic contraceptive agents are available, these cannot be used continuously due to their severe side effects (Aitken et al., 2008; Jain, Choudhary, & Jain, 2013). Hence, people are looking back to the age-old tradition of using herbal medicines, which have minimum side effects. A study was conducted to evaluate the *in vitro* spermicidal activity of a sapogenin (anagalligenone) isolated from *A. arvensis* whole plant. The results indicated the isolated compound to produce an immediate spermatozoal immobilization in 1 min (Mohamed, Ibrahim et al., Kamboj & Dhawan, 1982).

2.6.13. Miscellaneous activities

Besides above mentioned pharmacological effects, *A. arvenis* plant has been reported for different other therapeutical effects. For example, the plant has been reported for the ailment of the external parasite with Fidelity level of F1 = 100% (Bhatia et al., 2014), for treating eye inflammation (Viegi et al., 2003), haemorrhage (Cavero, Akerreta, & Calvo, 2013), skin diseases (López et al., 2013), wound healing (Cavero et al., 2013), as a sedative agent, and for bronchial asthma (Tiwari, 2008). Likewise, the whole plant has been studied for treating stomach gases in cattle (Kshirsagar & Singh, 2001). Moreover, acetyl saponins possessing anthelmintic activity have been extracted from *A. arvensis* (Singh, Kohli, & Parihar, 1955). Similarly, leaves of *A. arvensis* were reported for having an expectorant activity (Gairola, Gupta, Bansal, Singh, & Maithani, 2010).

2.7. Contraindications, toxicity and adverse effects

Regardless of the claimed medicinal uses of *A. arvensis*, the toxicological studies are of great importance. *A. arvensis* has been reported to cause poisoning in sheep. Sheep intoxicated with *A. arvensis* showed difficulty in breathing, gait stiffness, depression, weakness of the leg, recumbence and ultimately, sudden decrease in temperature followed by coma. Post-mortal lacerations included lungs and liver redundancy and also haemorrhage of the heart, kidneys, and intestines (Schneider, 1978; Stephens, 2002, pp. 75–134, Al-Sultan, Hussein, & Hegazy, 2003). Similarly, Al-Mujalli (2008) conducted a toxicity study of *A. arvensis* for one month in sheep and reported its toxicity in the daily dose of 5 g/kg BW. Mild clinical signs were observed, characterized by anorexia, restlessness, diarrhoea, thirst and increased respiration. There was a significant increase in the levels of alanine aminotransferase, glucose, and creatinine in comparison with pre-induction levels. Besides that, red blood cell, white blood cells, haemoglobin and packed cell volume were significantly lower than pre-induction values (Al-Mujalli, 2008). Likewise, four more cases of *A. arvensis* poisoning in cattle were diagnosed and reported by a research group in bristle fields of Department of Paysandu, Uruguay. The results showed 7–30% morbidity and 50–86% cases of fatality among different age groups of cattle (Riet-Correa, Rivero et al. 1998). In another report, gastrointestinal toxicity of this plant was reported in dogs and horses. It was also found toxic to poultry and rabbits and (the seed) to birds (Watt & Breyer-Brandwijk, 1962). Similarly, another study has been conducted on the toxicological parameters of the alcoholic extract of *A. arvensis* in rats for 15 days. The LD_{50} was 10.718 mg/kg BW (IP). *A. arvensis* toxicosis caused signs included anorexia, restlessness, diarrhoea, thirst, difficulty breathing, and tremors and ended by coma and death (Al-Sultan et al., 2003).

3. Conclusion and future directions

The present review paper reports for the fist time in a single compilation the folklore uses, phytochemical composition, toxicity and evidence-based pharmacological effects of *A. arvensis*. A comprehensive literature survey on the plant *A. arvensis* suggested it to be a vital medicinal plant employed in the treatment of hepatic, renal, diuretic, rheumatism, diaphoretic and expectorant complaints, epileptic attacks, mania, oedema, antifungal, and anti-inflammatory agent. Phytochemical studies conducted on the fresh plant materials, crude extracts and isolated components of *A. arvensis* stipulated a realistic validation of its various traditional uses. The evaluation of antimicrobial, cytotoxic, antioxidant, analgesic and anti-inflammatory activities have been done in recent studies that resulted in the justification of its traditional applications.

The ethnopharmacological and biological activity base studies on *A. arvensis*, along with the limitations and future directions has been summarized in Fig. 5. It has been found that some of its conventional uses like antimicrobial, amongst others have been extensively explored by several research groups. Among various geographical locations, different parts of the plant *A. arvensis* have been utilized in curing different diseases. The pharmacological studies that had yet been performed on *A. arvensis* were executed mostly on crude extracts. Therefore, the reproducibility of results and identifying the specific bioactive metabolite is very difficult. The need of the hour is to conduct bioactivity-guided isolation of bioactive metabolites and their standardization. However, in view of the colossal traditional uses and pharmacological potential of *A. arvensis* imply that a massive scope is still there regarding its phytochemical exploration. In order to assess the molecular mechanism and connection of naturally isolated drugs to the treatment of various diseases, further studies should be executed on the plant *A. arvensis*.

Author statement

Hammad Saleem; Sirajudheen Anwar, Nasser A. Awadh Ali: Conceptualization; Data curation, Methodology, Writing.

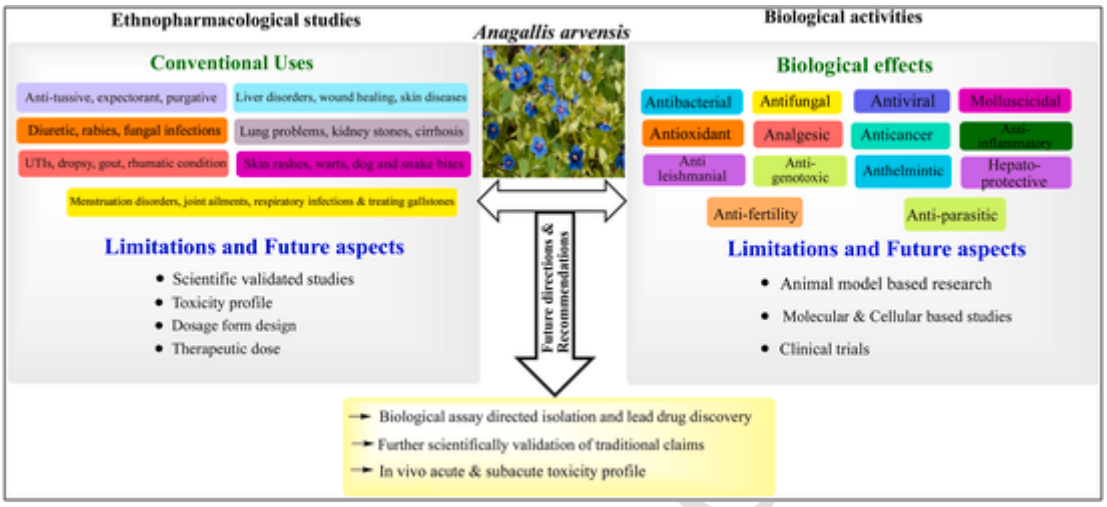

Fig. 5. The ethnopharmacological and biological activities studies on *A.arvensis*, limitations and future directions.

Muhammad Imran Tousif; Umair Khurshid: Writing - original draft.

Fawzi. M. Mahomoodally: Conceptualization; Writing - original draft.

Nafees Ahemad: Conceptualization; Data curation, Methodology, Softwar

Uncited references

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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