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Review

Chenopodium murale L.: A Weed of Medicinal Importance - A Brief Review

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Abstract

Weeds are considered a great threat to crops. So weed eradication is an important task to increase crop yield. Chemical weed control in various crops decreases their nutritive potential. To overcome this problem to some degree, it is suggested to use these weeds instead of destroying them. Keeping this in view, such losses can be compensated by exploring their medicinal utility and identifying their future medicinal prospects. *Chenopodium murale* L. (Amaranthaceae) is an annual weed growing throughout the world. This review aims to summarize the reported pharmacology and phytochemistry of *C. murale* to explore its medicinal utility and identifying their future medicinal prospects. The review was done by literature collection from textbooks and online databases without a time limit. The weed name was confirmed by 'The Plant List'. *C. murale* extracts, their isolated active constituents, and nanoparticles have been reported for various pharmacological actions like hepatoprotective, antihypertensive, antidiabetic, antidiarrheal, anticancer, antimicrobial, nematicidal, antioxidant, and cytotoxic. The pharmacological effects of *C. murale* may be due to the presence of secondary active metabolites such as phenolic acids, flavonols, terpenes and terpenoids, flavonoids and a steroidal glycoside. Reported phytochemistry and pharmacology suggest that *C. murale* could be an important medicinal agent for leishmaniasis, hypertension, infections and liver diseases. However, further studies are warranted.

Keywords: *Chenopodium murale* L; Weed; Ethnopharmacology; Phyto-constituents

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Introduction

Amaranthaceae/Chenopodiaceae is also known as goosefoot family. It contains about 174 genera and around 2,500 species of perennial or annual herbs, shrubs, and weeds. Some well-known members of this family are *Allenrolfea occidentalis* (S. Watson) Kuntze, *Atriplex polycarpa* (Torr.) S. Watson, *Chenopodium album* L., *Chenopodium murale* L. and *Dysphania ambrosioides* (L.) Mosyakin & Clemants. The current study is focused on *C. murale* which is commonly called Nettle leaf goosefoot in English [1], and Zurpikhin/ Jkheara in Arabic [2]. It is an erect, fast-growing annual weed. It contains 2-7 cm leaves and dull black, rounded, wrinkled seeds. It is widely distributed through the crops and waste places. Argentine Republic, Barbados, Brazil, Canada, Cyprus, Europe, Egypt, India, Mexico, Pakistan and Porto Rico are its cultivated areas [3]. It has high dispersal rate about (24,000 seeds/plant) due to large number of seeds. It affects vegetation through its adaptability in various environments and soil types [4]. It is widely known for its allelopathic effects on crops. It could exert its effects either as a stimulator [5], or an inhibitor for germination and growth for various crops viz. *Triticum aestivum* L. [6], *Hordeum vulgare* L. [4], and *Melilotus indicus* L. [7].

Eradication of weeds is a major concern for crop protection seekers. But the chemical weed control can decrease the nutritive potential. It is said that agriculturalists should give preference to alternative use of weeds over chemical weed control in an attempt to boost the crop's nutritive potential. In short, while we undoubtedly face problems of chemical weed control on our health, we must continue to explore other ways of weed control. Exploring the medicinal utility of weeds contribute to the economy with the effects they exert on a wide range of diseases [8].

In this regard, our study is focused on the medicinal importance of *C. murale*. *C. murale* is a widely used weed in Cyprus and Egypt. Aerial parts of *C. murale* are traditionally used in the treatment of dysentery [9], skin infections [10] and leishmaniasis [2]. Aerial parts are also used as pickles [11]. The weed is used as a potherb instead of spinach. It also possesses anthelmintic and laxative properties [12]. The trend of the use of *C. murale* as a reducing and capping agent for the synthesis of nanoparticles (NPs) is increasing continuously. Several studies reported the use of *C. murale* in NPs synthesis and its biological activities [1]. Moreover, *C. murale* is nontoxic as it showed no signs of toxicity at the dose 1600 mg dry extract /kg body weight [12]. A literature search showed that there is no review reported on *C. murale*, so we aim to review its phytochemistry and pharmacology to explore the medicinal potential of this weed.

Phytochemistry

Phytochemical studies on *C. murale* are as early as 1997 when Gohara, A.A. and M. Elmazar first isolated a hypotensive flavonoid glycoside from this weed [13]. The quantity of chemical constituents of *C. murale* varies based on different cultivated locations [11]. The weed contains phenolic acids [5], coumarins [14], flavonol glycoside [15], flavonol and flavonoids, terpenes and steroidal glycoside [11]. These chemical constituents might be responsible for the pharmacological activities of *C. murale*.

Table 1 summarizes the various compounds that have been reported from this weed. Compounds 1-8 belong to phenolic acids which are derivatives of cinnamic acid and benzoic acid. These compounds were extracted by headspace solid-phase micro-extraction technique and analyzed by gas chromatography-mass spectrometry (GC-MS). Although these phenolic acids are so similar, they are differing in the degree of methoxylation and hydroxylation of the aromatic ring. Phenolic acids are good antioxidants and are valuable for health [16].

Flavonoids are a ubiquitous group of naturally occurring polyphenolic compounds containing flavan nucleus. Structures 9 and 10 belong to flavonoids and are very similar, except that 9 contains two methoxy and one hydroxyl group in ring A, and the hydroxyl group on C-3 and 10 contains two hydroxyl groups and one methoxy group in ring A and methoxy group at C-3. Kaempferol (11) is 3,4',5,7- tetrahydroxyflavone, herbacetin (13) is 8-hydroxy kaempferol and kaempferitrin (14) is the 3,7-dirhamnoside of kaempferol. These compounds were extracted from ethanolic extracts prepared by maceration. The identification of compounds was done with thin layer chromatography (TLC) [17,18].

Compound 21 is a steroidal glycoside. Compounds 22-32 were analyzed as terpenes by GC-MS in the volatile samples of *C. murale*. Scopoletin (33) is the coumarin extracted by headspace solid-phase microextraction technique and analyzed by GC-MS from *C. murale* [11].

Pharmacological Activities

C. murale has reported antioxidant, antibacterial, antifungal, cytotoxic, hepatoprotective and antihypertensive activities. Table 2 and figure 1 described the pharmacological activities of *C. murale*.

Antioxidant Activity

Oxidation is a biochemical response that involves series of reactions leading to the production of free radicals harmful to human health resulting in various diseases [19]. Free radicals are exclusively sensitive

chemical substances consisting of such atoms which contain a free electron in their outer most orbit [20]. Free radicals are oxygen containing harmful molecules which are released during several degradation processes inside the body. These free radicals can damage the normal functioning cells of human body and can result in development of several disorders like ulceration, heart diseases, skin wrinkles, freckles and aging [21].

Antioxidants are substances that have ability to stop free radical-induced oxidation reactions. They can simply destroy free radicals, to reduce the damage caused by them. Antioxidants molecules either could be naturally produced inside the body, e.g. enzymes, bilirubin, albumin, ferritin, myoglobin, glutathione, and NADPH, or they can be exogenously ingested as a part of dietary substances e.g. vitamin C, flavonoids, β-carotene, vitamin E, thiols, vitamin A, and polyphenols. Medicinal Plants are the major source of antioxidants [22]. Aqueous extract and silver nanoparticles of *C. murale* leaves have marked antioxidant potential. Both have caused DPPH scavenging and β-carotene bleaching. Silver nanoparticles have only somewhat more potent antioxidant potential vs. aqueous extract of *C. murale* leaves. This shows that weed extract is responsible for antioxidant potential and silver nanoparticles are not contributing much. Silver nanoparticles could be prepared by physical, chemical and biological methods. Biosynthesis of nanoparticles by plant exceeds other biological methods due to its easiness [23]. A recent study indicated the antioxidant effects of chloroform fraction and ethyl acetate fraction of *C. murale* against DPPH and ABTS radicals. Saponins were found in high concentration in chloroform fraction.

Antibacterial Activity

Microorganisms like bacteria, fungi, viruses and parasites are the major cause of infectious disorders. Infections result from imbalance of host-pathogen interaction and alterations in environmental conditions [25]. Although antibiotic formulations have controlled infectious diseases, they are reported to have a number of side effects. The most important side effect of antibiotics is the development of resistant strains of microorganisms against the used antibiotic, hence same infection cannot be treated by the same antibiotic [26]. Medicinal plants could be a source of new antibiotics [27]. *C. murale*, being rich in various constituents, could be an option for the synthesis of new antibiotics. In this regard, various studies reported its antibacterial activity; however, there were no significant antibacterial effects reported in the literature. A study demonstrated the antibacterial activity of methanolic extract of *C. murale* of Mexican origin against several bacterial strains through agar dilution assay. Zone of inhibition and percentage inhibition against different bacterial strains of gastrointestinal tract viz. Escherichia coli, Shigella sonnei and Salmonella sp. were determined at 8 mg/mL or lower concentrations of *C. murale*. The standard control trimethoprim showed marked antibacterial potential (51.7–100% inhibition). However, the methanolic extract of *C. murale* could not show remarkable inhibitory potential (0 - 16.7% inhibition) [9].

Another study showed that *C. murale* ethanolic extract lacks antibacterial potential against *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *E. coli* [10]. These results are confirmed by a recent study that showed no antibacterial activity of *C. murale* against bacteria responsible of diabetic foot infection i.e., P. aeruginosa, *S. aureus*, *E. coli* and *Klebsiella pneumonia* [28]. The aqueous extract showed no zone of inhibition against *S. aureus*. However silver nanoparticles prepared form *C. murale* leaves have a small zone of inhibition against *S. aureus* [23]. Silver and gold nanoparticles have marked antimicrobial potential against a wide range of bacteria [29, 30]. So, the observed antibacterial effect against *S. aureus* was due to silver nanoparticles. Methanolic extract of *C. murale* flowers showed high zones of inhibition and low MIC values against Staphylococcus carnosus (Gram positive) and *E. coli* (Gram negative). Six mg streptomycin, 6 mg penicillin, and 25 µg amphotericin B in combination were used as standard antimicrobial products. The extract showed 13 mm and 15 mm zones of inhibition against S. carnosus and *E. coli* respectively; while the standard has 30 mm zone of inhibition against both strains. MIC values of the extract against both strains were 2.5 mg/mL; while the standard has 0.01 mg/mL. These results are conflicting as they are showing marked antibacterial activity of methanolic extract of *C. murale* against *E. coli* through disk diffusion and broth microdilution assays; while Ali et al., 2001 and Al-Hegami MA et al. 2016 showed no antibacterial activity of the methanol extract against *E. coli*. Moreover, standard antibiotics have more potent antibacterial effects as compared to crude weed extracts. It might be possible to isolate antibacterial constituents from the weed in the future but the crude extract lacks antibacterial potential.

Antifungal Activity

Antifungal drugs are used against a variety of pathological conditions caused by fungi viz. candidiasis, cryptococcal meningitis, ring worm, athlete's foot, fungal infection of nails, and aspergillosis. Methanolic extract of *C. murale* flowers showed 2.5 mg/mL MIC value against Saccharomyces cerevisiae; while standard 6 mg streptomycin, 6 mg penicillin, and 25 µg amphotericin B showed 0.03 mg/mL [2]. Roots and leaves methanolic and roots n-hexane extracts were

highly potent against Macrophomina phaseolina resulting in 84 - 90% decrease of fungal biomass. Order of decrease in fungal biomass by different extracts of *C. murale* was following:
n-hexane root extract > methanol leaf extract > methanol root extract> methanol stem extract >n- hexane inflorescence extract > methanol inflorescence extract >n- hexane stem extract >n- hexane leaf extract [3].

Cytotoxic Activity

Ethanolic extract of *C. murale* showed remarkable cytotoxic activity against FL-cells (a human amniotic epithelial cell line) using the neutral red assay. However, these results were not compared with any standard drug [10]. More research activities for its cytotoxic potential compared with standard drugs should be performed to confirm its cytotoxic potential.

Antiprotozoal Activity

Methanol extract of *C. murale* leaves showed significant antiprotozoal activity against Entamoeba histolytica (IC_{50} 90.3 µg/mL) and Giardia lamblia (IC_{50} 99.8 µg/mL). However, standard control metronidazole showed far greater antiprotozoal activity with IC50 of 0.04 and 0.21 µg/mL against *E. histolytica* and *G. lamblia* respectively [31]. Silver nanoparticles have reported antiprotozoal activity [30], so silver nanoparticles prepared form *C. murale* leaves should be investigated for their antiprotozoal potential to find their possible activity.

Nematicidal Activity

Methanol extract of *C. murale* flowers have nematicidal activity against *Steinernema feltiae*. Various extracts of *C. murale* showed significant nematicidal activity at lower concentrations even at 0.5 mg/mL. However, results were not compared with any standard nematicidal drug [2].

Antihypertensive Effect

In vivo study showed that kaempferol-3,7-dirhamnoside isolated from *C. murale* leaves at 45-135 µg/kg lowers the blood pressure in genetically prone hypertensive rats in a dose-dependent manner. The compound also lowered blood pressure and heart rate in normotensive rabbits in a dose-dependent manner. Kaempferol-3,7-dirhamnoside does not affect the blood pressure-lowering effects of nor-epinephrine in isolated guinea pig atria and aorta [13]. The study was interesting but weak point of study was a lack of comparison with standard antihypertensive drug.

Antidiabetic and Acetylcholinesterase Activities

A recent study indicated in vitro and *in vivo* antidiabetic effects of *C. murale*. Chloroform fraction of *C. murale* showed low IC50 value against glycosidase and significantly reduced *in vivo* blood sugar level. Similarly, chloroform fraction significantly inhibited acetylcholinesterase enzyme and improved memory in *in vivo* study [24].

Anticancer Effect

The extract of *C. murale* prepared by microwave-assisted extraction was evaluated for its anticancer effects against liver cancer (HACM) and breast cancer (MCF-7) cell lines. Cell cycle arrest and apoptosis were reported against both cancer cell lines [32].

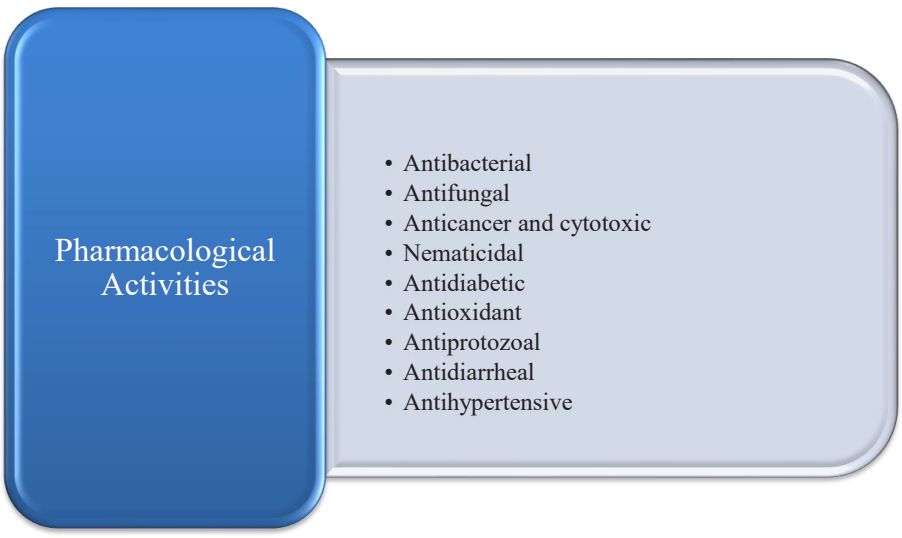
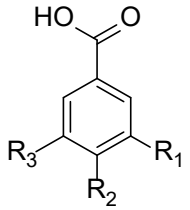
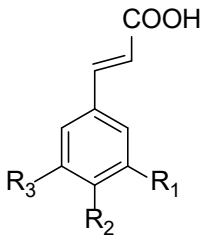
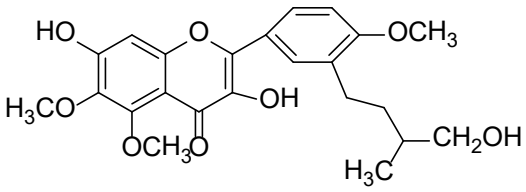
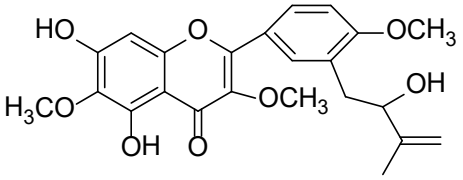
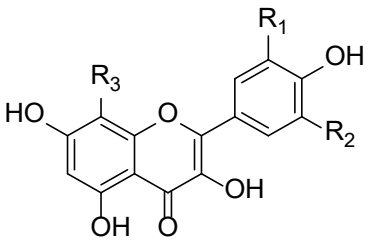
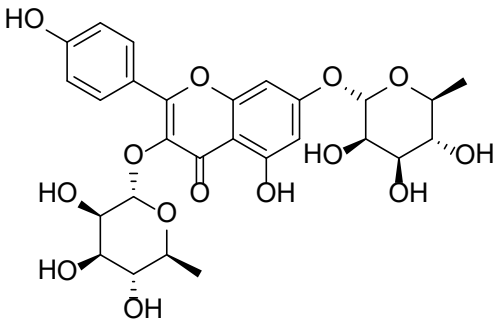


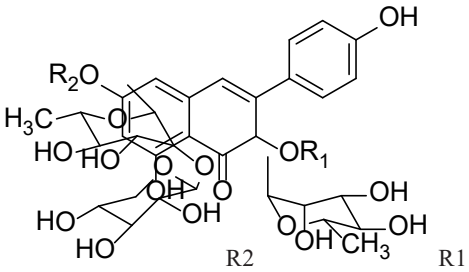
Figure 1. Pharmacological activities of *C. murale*

Table 1. Phytochemistry of *C. murale*

Structure	Chemical Compound name	References
Phenolic acids		
 1: R_1, R_2, R_3=OH 2: R_1= OCH_3 R_2= OH R_3= H 3: R_1, R_2=OH R_3=H 4: R_1, R_3=H R_2=OH	**1.** Gallic acid **2.** Vanillic acid **3.** Protocatechuic acid **4.** *p*-Hydroxybenzoic acid	[11,36]
 5: R_1, R_2, R_3=H 6: R_1=H R_2, R_3=OH 7: R_1, R_2=H R_3=OH 8. R_1=OCH_3, R_2=OH R_3=H	**5.** Cinnamic acid **6.** Caffeic acid **7.** *p*-Coumaric acid **8.** Ferulic acid	[11]
Flavonoids		
	**9.** 3, 7- Dihydroxy-3'-(4-hydroxy-3-methybutyl)-5,6,4'-trimethoxyflavone	[17]
	**10.** 5,7-Dihydroxy-3'-(4-hydroxy-3-(2-hydoxy-3-methyl-3-butenyl)-3,6,4'-trimethoxyflavone	[17]
 11: R_1, R_2, R_3=H 12: R_1=OH, R_2= H, R_3= H 13: R_1=H, R_2= H, R_3= OH	**11.** Kaempferol **12.** Quercetin **13.** Herbacetin	[18]

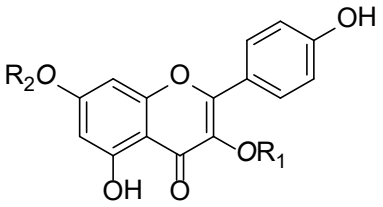


14. Kaempferitrin [11]



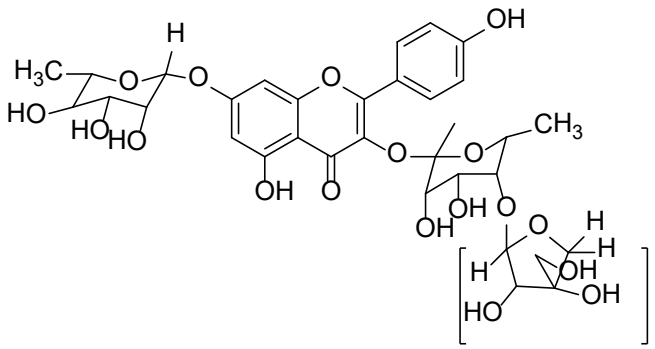
R2 R1

15. Kaempferol 3-*O*-α-L-rhamnopyranoside-7-*O*-β-D-xylopyranosyl (1→2)-*O*-α-L-rhamnopyranoside [37]



15: R_1= Glu R_2= Rha
16: R_1= Rha R_2= Glu
17: R_1= Rha R_2= Rha

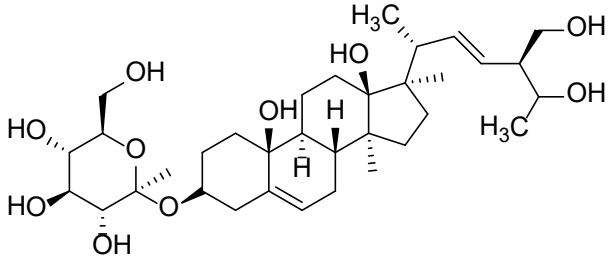
16. Kaempferol-3-*O*-β-D-glucopyranoside-7-*O*-α-L-rhamnopyranoside
17. Kaempferol 3-rhamnoside 7-glucoside
18. Kaempferol 3,7-di rhamnoside [37]



R_1= Api 18
R_2= Xyl 19

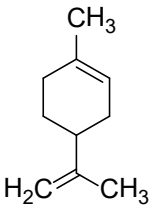
19. Kaempferol-3-*O*-{(4-β-D-apiofuranosyl)-α-L-rhamnopyranoside}-7-*O*-α-L-rhamnopyranoside
20. Kaempferol-3-*O*-{(4-β-D-xylopyranosyl)-α-L-rhamnopyranoside}-7-*O*-α-L-rhamnopyranoside [37]

Steroidal glycoside

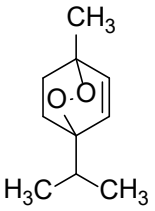


21. Stigmasterol 3-*O*-β-D-glucoside [11]

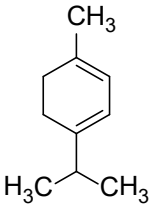
Terpenes



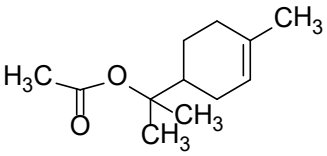
22. Limonene [11]



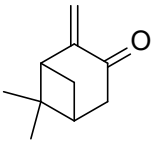
23. Ascaridole [11]



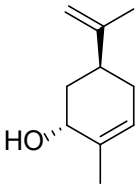
24. α-Terpinene [11]



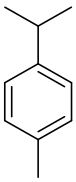
25. α-Terpinyl Acetate [11]



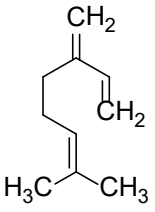
26. Pinocarvone [11]



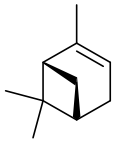
27. *trans*-Carveol [11]



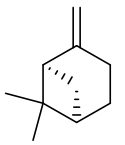
28. *p*-Cymene [11]



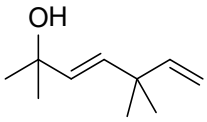
29. β-Myrcene [11]



30. α-Pinene [11]

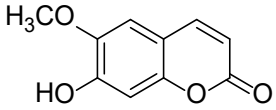


31. β-Pinene [11]



32. Yomogi alcohol [11]

Coumarin



33. Scopoletin [36]

Table 2. Pharmacological activities of *C. murale*

Pharmacological Activities	Extract type/ Compound	Experiment type	Dose	Major Findings	References
Antibacterial	Methanol Extract	*In vitro*	8 mg/ mL	40.5 mm zone of inhibition against *E. coli* while Trimethoprim showed 100 mm. 26.7 mm zone of inhibition *S. sonnei* while Trimethoprim showed 51.7 mm. 15.2 mm zone of inhibition *S. sonnei* while Trimethoprim showed 100 mm. 12.5 mm zone of inhibition *Salmonella sp.* while Trimethoprim showed 100 mm. 11.1 % inhibition against *E. coli* while Trimethoprim showed 100 %. 12 % inhibition *S. sonnei* while Trimethoprim showed 51.7 % 16.7 % inhibition *S. lexner* while Trimethoprim showed 100 %. 0.0 % inhibition *Salmonella sp.* while Trimethoprim showed 100 %.	[9]
	Methanol Extract	*In vitro*	MIC_{50} 2.5 mg/ mL	Against *S. carnosus* standard control (6 mg streptomycin, 6 mg penicillin, and 25 µg amphotericin B) showed 0.01 mg/mL.	
	Methanol Extract	*In vitro*	MIC_{50} 2.5 mg/ mL	Against *E. coli* while standard control (6 mg streptomycin, 6 mg penicillin, and 25 µg amphotericin B) showed 0.01 mg/mL.	[2]
	Methanol Extract	*In vitro*	2.5 mg/ mL	15 mm zone of inhibition against *S. carnosus* while standard control (6 mg streptomycin, 6 mg penicillin, and 25µg amphotericin B) showed 30mm.	
	Methanol Extract	*In vitro*	2.5 mg/ mL	13 mm zone of inhibition against *E. coli* standard control (6 mg streptomycin, 6 mg penicillin, and 25 µg amphotericin B) showed 30mm.	

Antifungal Activity	Methanol Extract	*In vitro*	4% v/w of extract	Stem extract inhibited 70% of *M. phaseolina* biomass.	[3]
	n-hexane Extract	*In vitro*	4% v/w of extract	Root extract inhibited 90% of *M. phaseolina* biomass.	
	Methanol Extract	*In vitro*	MIC_{50} 2.5 mg/mL	Against *S. cerevisiae* while standard control (6 mg streptomycin, 6 mg penicillin, and 25 µg amphotericin B) showed 0.03 mg/mL.	[2]
	n- butanol fraction	*In vitro*	100 mg/mL	reduced its biomass up to 98% over control	
Cytotoxic Activity	Ethanol Extract	*In vitro*	22 µg/mL	cytotoxic activity against FL-cells.	[10]ÿÿÿ
Antioxidant Activity	Aqueous Extract	*In vitro*	20 g/L	59.43% inhibition of DPPH. 51.13% inhibition of β-carotene.	[38]
	Silver nanoparticles	*In vitro*	20 g/L	65.43% inhibition of DPPH. 53.38% inhibition of β-carotene.	
Nematicidal Activity	Methanol Extract	*In vitro*	10 mg/mL	Significantly (<0.01) decreased viability of *S. feltiae.*	[2]
Antiprotozoal Activity	Methanolic Extract	*In vitro*	IC_{50} 90.3	Against *E. histolytica* while Metronidazole showed IC_{50} 0.04.	[31]
		In vitro	IC_{50} 99.8	Against *G. lamblia* while Metronidazole showed IC_{50} 0.21.	
Antihypertensive Activity	Kaempferol-3,7-dirhamnoside	*In vivo*	290 µg/kg	Reduced heart rate by 28.57 in normotensive rabbits. Reduced blood pressure by 31.58 mm/Hg in normotensive rabbits.	[39]
		In vivo	135 µg/kg	Reduced blood pressure by 57.1 mm/Hg in genetically prone hypertensive rats while initial blood pressure was 147±6.9 mm/Hg.	
	Mixture of flavonoids from *C. murale*	*In vivo*	20 µg/kg	Reduced heart rate by 33.34 in normotensive rabbits Reduced blood pressure by 41.05 mm/Hg in normotensive rabbits	

Antidiarrheal Effects

C. murale has ethnobotanical use in control of diarrhea. Astudillo-Vazquez et al. explored the antidiarrheal effects of *C. murale* [33].

Hepatoprotective Effect

Oral intake of high-dose paracetamol can induce hepatotoxicity in mice. However, *C. murale* aqueous methanol extract (250 and 500 mg/kg, p.o.) significantly reduced the levels of hepatic marker enzymes after 7 days of treatment. Moreover, disarrangement of normal hepatic cells with tissue necrosis, periportal inflammation, ballooning and dilation in sinusoidal spaces in mice were treated with *C. murale* aqueous methanol extract after intoxication by paracetamol [15]. Another study also reported hepatoprotective effects of *C. murale* in carbon tetrachloride induced hepatotoxicity in rabbits [34]. Quercetin, gallic acid and kaempferol present in the weed may contribute to its hepatoprotective effects.

Toxicology studies

C. murale acute and sub-acute toxicity studies showed no mortality and significant weight loss. However, in acute toxicity, *C. murale* significantly reduced hemoglobin and platelets. On histopathology, focal periportal hepatitis was observed during sub-acute studies. Such hepatotoxic effects contradict the hepatoprotective findings of previous studies conducted in 2014 [15,34]. This controversy in the activity should be explored in future studies.

Novel delivery systems for metabolites from Chenopodium murale

C. murale has complex metabolites and its transdermal delivery is a challenge. However, a recent study indicated that transdermal delivery of *C. murale* metabolites can be done through transethosomes while preserving its chemical structure. Furthermore, ethosomal vesicles allow entrapment of plant extracts

[35]. Hence, ethosomal vesicles of *C. murale* can also be synthesized.

Conclusion

The present review asserts the medicinal value of *C. murale* weed. In this regard, phytochemistry and pharmacological potential of *C. murale* extracts/isolated chemical constituents were studied. Reported phytochemistry and pharmacology suggest that *C. murale* could be an important medicinal agent for leishmaniasis, hypertension, and liver diseases. Phytochemical analysis of various parts of *C. murale* showed the presence of phenolic acids, flavonols, terpenes and terpenoids, coumarin, flavonoids and steroidal glycoside. The pharmacological potential reported in the reviewed papers may be due to these bioactive substances. Several studies only reported preliminary data on pharmacology of *C. murale*. It appears from reviewing the data that some studies showed contradictory results and may not offer reproducible data. Study protocols of the reviewed research papers were improperly described. So, replication of experiments is also difficult. Due to such lacks, confirmatory decisions can not be made on the medicinal utility of *C. murale*. However, presence of certain bioactive compounds and preliminary data on pharmacology explored that *C. murale* cater health benefits and it should be explored in future to serve as source of potential bioactive constituents.

Conflict of Interests

The authors declare that they have no conflict of interest.

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