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UNVEILING THE THERAPEUTIC PROSPECTIVE OF ACTIVE PHYTOCHEMICALS FROM *FAGONIA* SPECIES AND POTENTIAL ROLE OF ITS GREEN SYNTHESIZED NANOPARTICLES

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Abstract

The genus *Fagonia* of the family Zygophyllaceae consists of species, mostly distributed in tropical-subtropical or warm-temperate regions of the world in different environmental conditions. *Fagonia* is a convenient herbal medicinal plant with a wide range of therapeutic potentials against different diseases. Numerous studies conducted to explore herbal chemistry and biological functions of *Fagonia* species. *In vivo* pharmacological examination of *Fagonia* species revealed noteworthy characteristics like cytotoxic and anti-cancer potential. Novel chemical ingredients found in the species included flavonoids, alkaloids, terpenoids, vitamins, and nutritional components. Numerous researches conducted on *Fagonia* species has been compiled in this review study. Using references from significant databases, it comprises a thorough review of the literature about the therapeutic usefulness and bioactivities of several extracts identified from *Fagonia* species. The areas covered in current review reveal details about the immense medicinal value of the different components of *Fagonia* species, presence of bioactive constituents as well as therapeutic efficacy of nanoparticles synthesized by using *Fagonia* plant extract, illustrating the advantages of using nanotechnology and green synthesis nanoformulation of herbal plants.

Key words: *Fagonia* species, Therapeutic potential, Cytotoxicity, Antioxidant, Nano-formulations.

Introduction

Existence of complicated diseases such as cancer, neurodegenerative disorders, oxidative stress and cytotoxic complications has been increasing all around globe. Therapeutically effective strategies were needed to treat human malignancies (Kamal *et al*., 2021). To treat most of the disorders, drug interactions and unpleasant effects were major limitations in sense of clinical knowledge. Due to their broad applicability, therapeutic safety, efficacy, and clinical response related to anticancer activity, herbal medicines are now fascinating as essential components of anticancer and anti-inflammatory agents (Safarzadeh *et al*., 2014); (Zabita & Qaiser, 2011). Plants of *Fagonia* species have medicinal potential, particularly against tumors, according to various research-based evidences. Studies have been directed to assess the cytotoxic and antitumor potential of *Fagonia* species with a variety of therapeutic modalities (Dilbar, 2014).

The genus *Fagonia* belongs to the family *Zygophyllaceae*, contains almost 22 genera and nearly 250 species (Ali & Khan, 2021). *Fagonia cretica, F. arabica*, (as shown in Fig. 1) as well as *F. indica, F. schweinfurthii, F. laevis, F. bruguieri, F. mysorensis* are commonly found and widely distributed (Alamami *et al*., 2022). *Fagonia* species are called locally as dhamana, sehrai booti, sachi booti, and shoka. *Fagonia* species grow in a variety of environmental and habitational circumstances. Presence of bioactive phytoconstituents like flavonoids, terpenes, terpenoids, saponins, glycosides and alkaloids, in *Fagonia* species have therapeutic value and remarkably acting as anticancer, laxatives, anti-leishmanial, antidiabetic, antipyretic, and hepatoprotective agents (Puri & Bhandari, 2014). *Fagonia olivieri* is extensively used for the treatment of vascular, renal and hepatic disorders and also serves as an antioxidant, analgesic, anti-inflammatory and prophylactic herbal medicinal plant (Barkatullah *et al*., 2009).

Fig. 1. (A): *Fagonia arabica* whole plant, (B): *Fagonia cretica* aerial view. Fagonia plant seems to be green in color with light purple flowers and small branches with leaves. (Original picture captured by author).

Fagonia species are biologically applicable as a component of modern cancer treatments due to presence of potentially bioactive phytochemicals. For instance, *Fagonia indica* is used to cure a variety of illnesses in some Asian countries, including Pakistan and India. Active metabolites such as phenolics, flavonoids, tannins, alkaloids, triterpenoids and coumarins are amongst the most common

active constituents of *Fagonia indica* (Shaker *et al*., 1999). Bioactivity was evaluated by using crude extract of fresh plant of *Fagonia indica* to isolate quinovic acid and its some-other valuable byproducts (Saleem *et al*., 2014). As reported, *F. arabica* contains sulfated triterpenes, saponins, phenol and flavonoids. *F. Cretica* contains flavonoid glycosides and saponins. *F. Sinaica* consists of flavonol and glycosides. *F. microphylla* have flavonol glycosides and triterpenes. *F. indica* contains flavonoids, triterpenoid, steroidal glycoside and saponins. *F. Tenuifolia* possess flavonol glycosides. *F. thebaica* Boiss contains flavonol and glycosides and *F. glutinosa* Delile contains diterpenes, and flavonol glycosides (Alamami *et al*., 2022). A total of 14 compounds were found in the essential oil of *F. longispina*. alpha-curcumene (1.75%), germacrene D (4.22%), carvacrol 18.72%), elemicin (22.85%), trans geraniol (3.05%), and α-terpinine (2.74%) (Ziane *et al*., 2021). Isorhamnetin, kaempferol and quercetin glycosides were identified from the *F. indica* complex. Kaempferol glycosides are the primary compounds of the *F. bruguieri* and *F. indica*, according to the literature that was currently available on phytochemical composition of *Fagonia*, These flavonoids glycosides have been extracted from the n-butanol fraction extract of *F. indica* (Shaker *et al*., 1999). *Fagonia cretica* contained bioactive constituents that were effective against disorders that were either incurable or difficult to treat with negative side effects of synthetic drugs (Qureshi *et al*., 2016). With 50% ethanol plant extract of *Fagonia cretica* have the potential to be antioxidant and ethanolic fraction of plant extract has more potential against oxidative damage with some pharmacological activities (Yousaf *et al*., 2019). The phytochemical examination revealed that the methanolic extract of *F. olivieri* included alkaloids, cardiac glycosides, flavonoids and tannins. Cardiac glycosides, however, were not found in the ethanolic or n-hexane fractions of this plant extract (Shad *et al*., 2017). Alkaloids, cardiac glycosides, flavonoids and tannins in the methanol extract of *Fagonia cretica* served as the impetus for the plant elements of *F. olivieri* that were also reported in literature (Rashid *et al*., 2013b).

Extract of *Fagonia* plants can serve as stabilizing agent for formulation of green synthesis nanoparticles illustrating the advantages of using nanotechnology and green synthesis over the other methods. Active phytocompounds are biologically used for synthesizing nanomaterials which will be widely useful in future as an alternate therapy of synthetic drugs (Ullah *et al*., 2017). Nanoparticles made from the extract of *F. cretica* demonstrated potent antibacterial, antifungal, anticancer, antidiabetic, and cytotoxic properties (Kiani *et al*., 2022). Biocompatible nanoparticles formed by using plant-based substances (with enhanced pharmacological actives) can be used as nanomedicines, in the pharmaceutical industry. Nanoparticles of *Fagonia cretica* may be used bio medically to treat infections and abnormalities caused due to oxidative stress (Khan *et al*., 2023b). Targeted drug delivery agents, cosmetics and industrial products make them strong contenders in biomedical research. *F. cretica* extract contains potent bio-reducing agents and antioxidants (Rashid *et al*., 2013a). Additionally, different concentrations of the *F. cretica* extracts and silver nitrate ($AgNO_3$) mediated nanoformulations were used to produce nano particles with improved stability and with anti-inflammatory effects (Zulfiqar *et al*., 2019). The researchers suggested that phytochemicals of *Fagonia* herbal species as well as nanoformulations synthesized by using *Fagonia* extract showed therapeutic potency but further *In vivo* studies are required to check these therapeutic drug potential (Rahman *et al*., 2021).

Numerous investigations have been carried out to explore pharmacological activities of this plant, but to the best of our knowledge, a review article is required to compile reported potential and therapeutic role of *Fagonia* species. This review highlights the therapeutic advantages, medicinal value, and significance of *Fagonia* plant and its synthesized nano-formulations used in various disorders. Utilizing search engines including Google Scholar, Scopus, PubMed, Science Direct, Elsevier and Molecule, a review of the biological activity, photochemistry, medicinal potential, and pharmacological significance of *Fagonia* was carried out. In this review, the literature from the years 1999 through 2022 was gathered. The keywords used during searching of literature included *Fagonia* species, therapeutical value, potential activity, cytotoxicity, antioxidant, antitumor activity, nano carriers alone and in diverse combinations. The knowledge about *Fagoni*a species with validated *In vivo* or *In vitro* studies on multiple diseases is the special subject of interest for this review.

Therapeutic and pharmacological significance

Anticancer potential of *Fagonia* extract and nanoparticles: *Fagonia indica* may be a source of naturally occurring chemicals with cytotoxic effects against cancer by inhibiting epidermal growth factors, tyrosine or proliferators triggered receptor proteins of peroxisome (Javed *et al*., 2021). Aqueous extract of *Fagonia cretica* induced apoptosis via p53-dependent as well as cell cycle independent mechanisms and coupled by DNA damage response activation. A study demonstrated that *FOXO3a* (protein coding gene over expressed in tumors) performed important anticancer action in the absence of p53. It was also reported in literature that *F. cretica* extract contains multiple cytotoxic, anti-inflammatory and anti-cancer agents which work against cancer metastatic action via DNA damage and induced *FOXO3*a gene expression to suppress tumor responses and p53 expression (Lam *et al*., 2012).

The potential of quinovic acid (phytochemical obtained from *Fagonia indica*) was investigated for anticancer activity. Literature finding's indicated that quinovic acid (QA) blocked the growth and metastasis of breast and lungs cancer. Quinovic acid is very specific for suppression of cancer cells and viability as associated to healthy cells. It also potentiates anticancer effects, as accompanying with stimulation of cell apoptosis linked with activation of caspases 8 and caspase 3 and stimulation of death receptor 5 (DR5). DR5 ligand also potentiated the anticancer effects, exhibited that QA exerts its anticancer effects via a bioactivity-guided fractionation strategy, and the *In vitro* effects of the resulting organic fractions on breast cancer (BC) cell lines MCF-7 and MDA MB-468

were examined and showed marked cytotoxicity effects. QA enhanced DR5 mRNA and protein stabilities but had no impact on the promoter activity. QA induces apoptosis by activating a pathway dependent on DR5 to exert its anticancer effects, (Khayam *et al*., 2020). Kiani *et al*., (2021) demonstrated similar findings that *F. cretica* exerted cytotoxic activity, where cytotoxicity was evaluated by using *F. cretica* (aerial parts) crude extracts and nanoparticles formulated by *F. cretica* extract in brine shrimp larvae. Comparing crude extracts of *F. cretica* to ZnO NPs, a considerable cytotoxic effect was observed (Kiani *et al*., 2022). Halawani (2021) demonstrated antibacterial and antitumor activities of *Fagonia bruguieri* (Shaoka) against human hepatocarcinoma (HepG2) and breast cancer (MCF-7) cell lines. The selected honey exerted cytotoxicity on both cancer cell lines, inhibiting cell proliferation rate and viability percent in HepG2 and MCF-7 cancer cells. These results confirmed the potential use of *F. bruguieri* as a remedy and introduced a new template for treating infectious disease and cancer (Halawani, 2021).

Potential against breast cancer: Some steroidal saponin glycosides obtained from *F. indica and F. schweinfurthii* extract were separated through fractional process and tested against breast cell lines MDA-MB-468 and MCF-7. These purified compounds exhibited cell specific anticancer activity and showed prompted apoptosis in low concentration on MDA-MB-468 but a substantial episodes of necrosis in MCF-7 cells was observed exhibiting the therapeutic response of the purified compounds from *Fagonia* species (Waheed *et al*., 2012). These observations were also in accordance to Lam *et al*., (2012) who reported that *F. cretica* extract showed dose-dependent cell cycle arrest, antiproliferative action and stimulated apoptosis in breast cancer cell lines MCF-7 and MDA-MB-231. Hussain *et al*., (2007) reported laboratory investigation using antineoplastic, cytotoxic, anticancer, anti-tumor and DNA damage assays and revealed the therapeutic potential of *Fagonia cretica*. While anticancer assay showed that *Fagonia cretica* extract prevented tumor orientation on potato discs as well as its cytotoxic effect was clearly detected against brine shrimps at a concentration of 118.89 ppm. With determined tumor inhibition of roughly 77.04% against *Agrobacterium tumefaciens* strain10, significant anticancer effects were also observed against all tumor-inducing strains of this pathogen (Hussain *et al*., 2007).

Biosynthesized AgNPs made from *F. indica* were examined to observe cytotoxicity, using the MTT cell viability assay. Outcomes showed that the concentration of AgNPs had an impact on the growth of breast cancer cells. The apoptotic assay, DAPI assay and Annexin V/PI flow cytometric assay was used to examine changes in cellular nuclear morphology and to observe apoptotic activity. In response to the *F. indica* mediated nanoparticle's treatment, the cells showed disrupt morphology, had an unnaturally bright color, aberrant nuclei, compacted chromatin, and an uneven cell shape. The impact of green nanoparticles on MCF-7 cell lines was also previously studied by Walimbe *et al*., (2022) who clearly demonstrated the anti-proloferative activity of *F. indica*.

Potential against hepatic cancer: Hepato-protective activity of *F. indica* as well as molecular mechanisms involved in treatment of hepatic injury was reported by Azam *et al* in 2018. Thioacetamide was used to cause liver damage in the mouse model, which was followed by the administration of *Fagonia* extract. Treatment of liver functions in mice treated with *F. indica* plant extract revealed indications of changed expression of hepatic markers and proinflammatory markers IL-1, IL-6, and TNF-a. *F. indica* significantly regulated the expression of genes related to innate immunity, including toll-like receptors 4 and 9, suggesting a possible role for the plant extract in immune regulation to treat liver injury (Azam *et al*., 2018). Treatment with *F. schweinfurthii* ethanolic extract (FSEE) decreased the rise of AST, ALT, and ALP levels and prevented decrease in total serum protein levels in rats, along with significantly decreasing cell growth in the CCl_4-induced tumor in HepG2 cells. Studies on histopathology confirmed that FSEE has a protective effect against oxidative damage (Pareek *et al*., 2013). Javed *et al*., (2021) described an *in-silico* investigation of the *F. indica* plant, which showed the extraordinary potential for cancer therapy via structural based drug design of innate biomolecules against target proteins. Five proteins were employed in this study: apoptosis proteins, mutant EGFR kinase crystal structure, Bcl-xl crystal structure, apoptosis regulator protein MCL-1 BH_3 and epidermal growth factor protein, were docked against approximately 134 ligands selected from the literature. The cancer cell lines HeLa shows highest score in the *in-silico* investigation. HeLa, human carcinoma cell lines were also exposed to *In vitro* cytotoxic effects exhibited by *F. indica* plant, which had an IC_{50} of 28.3± 0.102 µg/ml (Javed *et al*., 2021).

Triterpenes, saponins and five other types of reported phyto-chemicals were isolated and identified first time from *F. schimperi*. The antibacterial, oxidative, and cytotoxic therapeutic effects of crude saponins and ethyl acetate fraction (of the plant extract) were assessed. Saponins and the ethyl acetate fraction had the strongest anti-hepatic and anti-cancer activity. However, hepatocellular carcinoma was found to be resistant to the powerful anti-proliferative effects of the ethyl acetate fraction (Howayda *et al*., 2020). These results were slightly comparable to Yousaf *et al*., (2019) who reported synthesis of AgNPs of *F. cretica* by double dip dilution methods and identified the bioactive components that were involved in their synthesis. Bioactivities like anti-oxidant, anti-tyrosinase, and anti-urease activity was successfully employed to synthesize silver nanoparticles by using 50% fractionation of *F. cretica*. Whereas the anti-tyrosinase and anti-urease activity of plant extract was observed to be more powerful with 90% and 70% ethanol fractions, respectively. With 50% ethanol plant extract, it exhibited potential to be antioxidant and perform urease-inhibiting activity.

Antitumor potential: Crude saponin fractions from *Fagonia indica* that were examined against cell lines HepG2 and MCF-7 for their antiproliferative effect and antitumor potential. The isolated chemical showed very potent cytotoxic activity with IC_{50} values of 8.18, 0.9 and 19.20 1.4 mg/ml, respectively. The ethyl acetate fraction showed potent anti-proliferative activity towards cell lines

HepG2 and MCF-7. The synergistic activity of flavonoids and triterpene saponins present in the plant extract has been demonstrated for the significant cytotoxic effect on several cell lines (Shaker *et al*., 1999). When *Fagonia arabica* extract was applied to the oral squamous cell carcinoma (OSCC) treatment by using SCC-4 cell lines, it caused apoptosis, which in turn inhibited cell proliferation. The G_0/G_1 phase of the cell cycle was halted, indicating a strong anti-carcinogenic impact of the *Fagonia arabica* extract on OSCC (Abou El-Nil *et al*., 2023).

Neuroprotective potential: Total antioxidant potential and phenolic content of *Fagonia olivieri* was measured using DPPH assay and a thorough study of ferric reducing ability of plasma (FRAP) tests and their unique energy metabolism was conducted. Reduced ATP levels in cells resulted higher lactic acid content in the blood and were indicative of ischemia, harm to red cells that resulted due to reduced energy status. *Fagonia arabica* have neuro-protective potential and provided significant protection from cell damage as well as ischemia to maintain the cellular stability and mitochondrial integrity of the cells, demonstrating that *F. arabica* possessed a significant amount of antioxidant activity (Rashid *et al*., 2016a). *Fagonia cretica* increased the expression levels of γ-GCS genes, although partial differences in the response towards γ-GCS gene expression were observed according to the dose and the constituents existing in *Fagonia cretica*. *Fagonia cretica* could directly interact with free radicals and the results were more apparent for OH radicals. Although direct foraging of the free radicals is an imperative mechanism so far drugs may exert their cytoprotective consequence by preventing the free radical mediated tissue damage (Rawal *et al*., 2004).

Anti-ulcer potential: Many natural products and medicinal plants extracts have been used for protection against peptic ulcer as it is believed that organic natural compounds have healing strategies with minute impairment. A number of advanced studies were accepted to investigate protective effects of *Fagonia indica* alcoholic extract against ulcer diseases in contrast to effects of natural honey solution of ethanol (Mahdy *et al*., 2018). Khayam *et al*. reported that by directly lowering peroxides, scavenging free radicals, and promoting the activity of antioxidant defense enzymes, pharmacological activities of *Fagonia* species advantages are allied to their antioxidant qualities. Flavonoids identified from *Fagonia* species have cytoprotective properties and their anti-ulcerogenic efficacy has also been investigated. It was reported in previous literature that flavonoids derived from the *Fagonia* plant, particularly quercetin (found in alcoholic extract of *Fagonia indica)*, protected against alcoholic induced stomach, duodenal and esophageal ulcers. The production of mucus being increased by quercetin and its glycoside, is thought to be a necessary effect for reducing gastric lesions (Khayam *et al*., 2020).

Antidiabetic potential: The pronounced effect of *Fagonia indica* extracts alone and in combination with some other herbal plant on alloxan-induced hyperglycemia in mice was investigated by Mahdy & Shehab (2015). At first, mice was treated intraperitoneally with alloxan monohydrate about 150 mg/kg to raise glucose in blood. Mice having blood sugar levels above 250 mg/dl were designated hyperglycemic, and *F. indica* at a dose of 500 mg/kg was administered according to experimental protocols. Blood sugar levels were significantly reduced after 15 days and it may be concluded that *Fagonia indica* can act as glucose reduction mediator (Mahdy & Shehab, 2015). Another *in silico* study found that α-glucosidase obtained from extract of *F. cretica* and *F. sativa* was therapeutically used to treat diabetes. Testing have long been utilized as anti-diabetic agents and various studies have been carried out using extracts of *F. sativa*. Testing was done on *F. cretica* against α-glucosidase along with extracted phytochemicals from these plants were computationally screened to identify active ingredients (Rahman *et al*., 2021). The researchers then deduced from the results that phytochemicals of such herbal plants showed therapeutic potency but further *In vivo* studies are required to check these therapeutic drug potential. *F. cretica* extract significantly ($p<0.05$) upgraded renal functions, blood parameters, total protein, enzymes and albumin, which indicated that *Fagonia* had therapeutic efficacy to reduce renal abnormalities. Moreover, literature suggested that these herbal compounds prevented developing nephropathy, hepatic incompetency and end-stage renal illness. Antidiabetic and anti-protective action of plant might be responsible for amelioration of kidney impairment. As it is claimed that it contained flavonoids, glycosides, aldehydes such as naringin, kaempferol, limonene, geraniol and lycopene that act as anti-oxidant, anti-inflammatory agents to reduce hyperglycemia and to prevent spontaneous kidney damage (Kamran *et al*., 2017).

Thrombolytic potential: *F. arabica* have thrombolytic properties that could help in lysing of blood clots in *In vitro* models but studies on *in vivo* clot dissolving properties were not fully understandable because active components of *Fagonia arabica* having clot lysing properties were yet to be investigated (Lam *et al*., 2012). *F. arabica* could functionally act as thrombolytic agent for patients suffering from atherothrombotic diseases (Prasad *et al*., 2007). It is also reported that in addition to breaking up clots and fibrin fibers (that bind cells together and cause clotting in cells), flavonoids and terpenes present in *F. arabica*, activates plasminogen, which further leads to clot dissolution (Parry *et al*., 2000).

Coagulation factors impact the risk of venous thrombosis and stimulation of unhealthy factors such as oxidation in cells, ageing, inflammation, heart disorders and protein C deficiency (Prasad *et al*., 2007). According to earlier report *F. arabica* (Dhamasa) functions as a thrombolytic medication and exhibits significant proportion of clot lysis ability. To fully understand their medicinal potential, more investigations related to phytochemical effects will be required. Following scientific validation, these herbal remedies function as thrombolytic agents to treat the condition of patients with atherothrombotic or vascular illnesses (Chaudhary *et al*., 2015).

Potential against skin diseases: All plant parts of *F. schweinfurthii* were boiled and extract obtained after boiling was potentially used for allergies, infectious wounds and various acne problems as well as the decoction can be administered orally as a blood antiseptic. When applied topically, the powder of the complete plant heals boils and skin eruptions. Aqueous extract of another species *F. bruguieri* has been utilized for its anti-allergy properties. Anti-inflammatory and anti-allergic properties were some of the additional effects of *Fagonia* species including skin diseases and wound healing (Puri & Bhandari, 2014). The effect of *F. schweinfurthii* gel on wound healing was examined by applying 0.5 g/wound of the gel once daily for 19 days to the albino rats' excision wounds, with observations made every alternate day. It has been shown that gel formulations quicken the healing process and have a gradual anti-inflammatory impact. This investigation revealed the possibility of developing a gel formulation of *F. schweinfurthii* plant extract as a medicinal agent with anti-inflammatory and wound-healing properties (Saleh, 2011). *F. cretica* was specifically used for treating a variety of disorders related to blood, arteries, skin, and digestive tract as reported in literature (Sharma, 2019). The plant was given as herbal tonic and has been extensively (prophylactically) used for the treatment of smallpox in children. It contains cooling properties and is used in skin diseases, particularly its leaves and twigs are used (Alamami *et al*., 2022).

Effect on endocrinological parameters: Anti-carcinogenic potential of freshly prepared extract obtained from *F. cretica* and activity of some of isolated triterpenoid saponins was identified while investigating the effect of *F. cretica* on rabbit's endocrinological parameters (serum thyroxine, serum prolactin, serum proteins and serum cortisol). These saponins significantly lowered thyroxine levels and prolactin levels at dose rates of 30 mg. Saponin-I exhibited non-significant effect on thyroxine after 16 days, saponin-II dramatically diminished the amount of serum thyroxine when given up to 30 mg. According to the results, saponin-II caused the greatest increase in blood cortisol after 16 days. This was because of the presence of saponin-II molecule seems to be involved in this action (Saeed *et al*., 2003). The significance of nanoparticles reported the green synthesis of AgNPs from extract of leaves of *F. cretica* and were the subject of a study that assessed the anti-diabetic properties of the generated AgNPs *In vitro* and *In vivo*. Four sets of 20 male Balb/C albino-mice were used for the *In-vivo* experiments. Research using *In vivo* anti-diabetic models revealed a satisfactory increase in body weight together with a decline in all metabolic markers (Khan *et al*., 2023a). *In vitro* and *In vivo* tests revealed that the *F. cretica* silver naonoparticles (FcSeNPs) showed antioxidant, anti-diabetic and anti-hyperlipidemic properties. Enzymes including α-glucosidase and α-amylase, as well as free radicals like DPPH and ABTS, were effectively inhibited by the FcSeNPs. Anti-hyperglycemic impact was found in *In-vivo* experiments at a dose of 2 mg $kg^{-1,}$ which was significantly less than that of the conventional medication metformin (200 mg kg^{-1}) (Khan *et al*., 2023b). As demonstrated by the concentrations of biochemical indicators for the pancreas, liver, and kidney, the FcSeNPs also had positive impacts on these organs (Khan *et al*., 2023). Kiani *et al*., (2022) investigated that, with an IC50 value of 35.10 µg/ml, the maximum free radical scavenging activity was reported by *F. indica* NPs generated from ethyl-acetate extract. NPs' polar solvents showed prominent antibacterial action against *Bacillus subtilis, Escherichea coli,* and *Klebsiella pneumonae* cultures. Nanoparticles produced from methanol extract had a substantial antidiabetic efficacy of $52.61 \pm 0.36\%$. This study emphasized how important *F. indica*, and serve as a natural source of functional nanoparticles with significant antibacterial, cytotoxic, antioxidant, and protein kinase inhibitory effects, as well as antidiabetic capabilities (Kiani *et al*., 2022).

The therapeutic potential of *Fagonia cretica* and major saponins (saponin-I and saponin-II) present in it were studied to evaluate their effect on endocrinological parameters by Asif & Sabir, 2003. The two primary triterpenoid components were isolated from the plant's ethanolic extract using silica gel chromatography. Prolactin serum level, thyrotropin and cortisol, were examined in rabbits. Both saponins were given in dose of 30 mg, and this considerably reduced the levels of thyroid stimulating hormone (TSH) and prolactin relative to crude drug fraction and as observed in control groups. When compared to the crude medicine and saponin-I, the saponin-II significantly reduced the level of thyroxine after 16 days (Asif & Sabir, 2003).

Hepato-protective potential: Herbal extract of *F. oliveri* had significant hepato-protective activity in specified dose dependent manner by reducing the elevated level of biochemical parameters such as hepatic enzymes abnormally elevated by toxicity induced by CCl_4, 70% hepato-protective activity was detected due to presence of flavonoids, alkaloids, saponins and tannins present in *F. oliveri* extract (Rashid *et al*., 2016b). Serum levels of some parameters ALT, AST, ALP, total bilirubin were significantly increased in rats having CCL_4 induced toxicity related in contrast to normal control animal group but the methanolic extract of *F. oliveri* (400 mg/kg) treated rats showed maximum reduction of hepatic parameters in a substantial manner. Histopathological studies also revealed the hepato-protective benefits of methanolic extract of *F. olivieri* in dose dependent manner. These results suggest that different doses of *Fagonia* exhibit significant hepato-protective activity and this is because of flavonoids, alkaloids and tannins, specifically isolated from *Fagonia* extract (Rashid *et al*., 2016c).

Antileshmanial potential: A study observed cell viability by conducting a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay, that revealed that nanoparticles made from *F. indica* extract could exhibit antileishmanial activity (Ullah *et al*., 2017). A concentration dependent growth suppression was noticed after 24 hours of *F. indica* extract containing nanoparticles' administration. The IC50 values against promastigotes of *Leishmania infantum* were determined to be 19.42 ± 2.76 µg/ml for AgNPs of leaves extract, 30.71 ±1.91 µg/ml for stem mediated AgNPs and 51.23 ± 2.20 µg/ml for chemically produced AgNPs (Ullah *et al*., 2017).

Hamidi *et al*., reported the antibacterial activity of *F. longispina* extracts against *Salmonella heidelberg*, and *Escherichia coli*. The antibacterial activity of *F. longispina* essential oils was found to range from moderate to high. The chemical makeup of the essential oil, which is high in oxygenated molecules, may be the cause of this antibacterial effect (Hamidi *et al*., 2014). Biogenic nanoparticles could be employed as a potential substitute for chemically produced silver nanoparticles in the development of antileishmanial medications since they were more efficient, less expensive, stabilized, environmentally benign, and easy to synthesize (Ullah *et al*., 2018). In comparison to other studies, it was investigated that silver nanoparticles created from the leaf extract of *F. indica* may be another secure antileishmanial medication. AgNPs produce nitrogen oxide free radicals and that the infectivity of parasites equally decreases in comparison to control group after macrophage activation. These radicals induce oxidative stress in cells, decreases metabolic activity and ultimately leads to the death of cells and tissues at numerous sites (Farhana *et al.,* 2024). Furthermore research was needed in order to analyze the principal component of *F. indica* extract and its silver nanoparticles (Ullah *et al*., 2017).

Antimicrobial potential: Study conducted by Khattak, 2012 indicated antimicrobial activity of *Fagonia arabica* (root, stem and leaf) against bacterial and fungal strains by preparing extracts with organic compounds. All extracts showed sensitivity against microorganisms whereas *Escherichia coli* and *Streptomyces* were bacterial species designated for study, and the fungal species used were *Candida albicans* and *Trichoderma Ressie* (Khattak, 2012). It was also concluded that anti-parasitic, antibacterial activity and antifungal activities exhibited by methanolic and chloroform extract of roots, leaves and stems of *F. cretica*. The root and stems contain maximum amount of antibiotic property against various pathogens and were very effective against microbial infections (Sharma, 2019). Puri & Bhandari (2024). explained the antimicrobial activity of *F. cretica* and its isolated active constituents. Isolated compounds from methanolic extract of whole plant of *F. cretica* including linoleic acid, β-sitosteryl-3-O- β -D- (6-hexadecanoyl)-glucopyranoside), oleanolic acid and 23-hydroxy ursolic acid. These compounds showed significant antimicrobial activity against *Staphylococcus aureus*, *Escherichia coli*,, *Salmonella typhi* and *Candida glabrata* (Puri & Bhandari, 2014). The anti-microbial action of aqueous extract of *Fagonia indica* leaves was evaluated. (Sharma *et al*., 2013). The leaf extracts (25, 50, and 100 mg/ml) were examined for their ability to suppress the growth of both gram-negative and gram-positive bacterial strains. It was observed that ethanolic extract had significantly inhibited all the strains of bacteria, and that its inhibitory activity was found to be greatest against bacterial strain *Bacillus cereus* and least against *Pseudomonas aeruginosa*. Ethanolic and water extracts had shown exhibiting significant ($p<0.05$) analgesic activity (Sharma *et al*., 2013).

Mariam *et al*., (2021) reported potential of NPs compared to commercially available control medications, where large concentrations of prepared *Fagonia cretica* gold nanoparticles (FGNPs) were both less toxic and more effective. The purpose of this experiment was to determine how well FGNPs worked as antibacterial agents in contrast to antibiotics, which served as control group (Mariam *et al*., 2021). These results also supported earlier findings concluded that, *Proteus vulgaris, Escherichia coli,* and *Klebsiella pneumoniae* were all successfully inhibited by *Fagonia cretica* AgNPs. In comparison to *Escherichia coli* which caused cell toxicity, it was discovered that AgNPs produced the highest amount of reactive oxygen species (ROS) in *Proteus vulgaris* (Zulfiqar *et al*., 2019). The ethyl acetate fraction of *F. olivieri* have antibacterial properties that can be accounted for by their chemical composition. The results shown that *E. coli* strains were most susceptible compared to others. For several *F. indica* preparations, the extract and its varied fractions also exhibited diverse antibacterial properties due to the presence of different bioactive ingredients such as alkaloids, flavonoids and saponins (Rashid *et al*., 2019). GNPs were examined for their biomedical applications, specifically their antibacterial properties against *E. coli* and cocci shaped bacterial species. Their results claimed that prepared GNPs may have significant antimicrobial applications, environmental friendly and their ability to emit light might suggests using them as possible biomarkers (Mariam *et al*., 2021).

It is crucial to investigate the level of reactive oxygen species (ROS) production due to presence of different bacterial strains (*Escherichia coli* and *Klebsiella pneumoniae*) by using different concentrations as 5, 10 and 20 µg of Ag-NPs, ciprofloxacin and plant extract to determine level of toxicity. Formation of ROS also increased in all bacterial strains when the concentration of Ag NPs of *Fagonia cretica* and was increased steadily 5 µg/ml to 20 µg/ml, showing that the ROS production was fully dependent on dose of extract to be used. The results of ROS calculations have shown that Ag NPs are considerably more operative against *Proteus vulgaris* than *Escherichia coli* and *Klebsiella pneumoniae. F. cretica* plant extract marginally boosted the generation of ROS, its concentration did not significantly change ROS levels (Zulfiqar *et al*., 2019). These results were also in accordance to study by Kiani *et al*., (2022) who used *F. cretica* extracts and assessed their phytochemical composition and range of their biological activities. Methanol, n-Hexane, aqueous, and ethyl acetate were 4 different solvents that had been used in the extraction process. NPs made from ethyl-acetate extract exhibited the highest levels of free radicals scavenging activity. The polar solvents in formulations of nanoparticles exhibited significant antibacterial activity against *B. subtilis, E. coli,* and *K. pneumonae*. The LC50 value of *Fagonia* NPs generated from hexane extract against brine shrimps was 42.41µg/ml, indicating possible cytotoxic action (Kiani *et al*., 2022).

Anti-inflammatory potential: The initial reaction to injuries and wounds, whether internal or external, is inflammation. Mansoor *et al*., (2022) reported the used biological method to create the *F. Arabica* silver and graphene oxide doped manganese oxide nanocomposites (MnO-GO-Ag) and tested their capability to reduce inflammation. The goal of NPs synthesis was to get rid of the negative effects of synthetic medications and to develope conventional nanocomposite manufacturing,

green nanocomposite that has larger potential to alleviate inflammation. Compared to ascorbic acid, MnO-GO-antioxidant Ag's activity exhibited a greater scavenging capability. The MnO-GO-Ag NCs displayed percentage inhibitions for anti-inflammatory activity of 34.15 and 81.71%, with IC_{50} values of 0.15 and 0.23, at 0.1 and 0.5 mg/mL concentrations, respectively. Lower IC_{50} values for the MnO-GO-Ag NCs demonstrated the strong effectiveness of the NCs for anti-inflammatory and antioxidant actions (Mansoor *et al*., 2022).

Antioxidant potential: Isorhamnetin, kaempferol and quercetin glycosides are identified from the *F. indica* complexes. Kaempferol glycosides were the primary compounds of the *F. bruguieri* and *F. indica.* These flavonoids glycosides have been extracted from the n-butanol fraction extract of *F. indica* (Shaker *et al*., 1999). According to a study, *F. arabica* has anti-oxidative properties and are effective at preventing cell death brought on by ischemia and reperfusion. Thus, *F. arabica* may serve as a preventative agent for the handling of ischemic stroke (Satpute *et al*., 2012). It was reported that *F. olivieri* may serve as organic source to produce free radical scavengers that can be helpful in reducing the oxidative tension. The content of phenolic, alcoholic and flavonoid chemicals (present in the plant extract) and the antioxidant activity were significantly correlated and suggested that these molecules were involved in antioxidant activity (Rashid *et al*., 2016). Atiq-ur-Rehman *et al*., (2019) in their study indicated the incidence of various phytochemicals in alcoholic and methanolic extracts of *F. cretica* and *F. indica*. *Fagonia's* chloroform extract primarily included polyphenols and flavonoids. The methanol extract exerted α-glucosidase inhibitory activity with a half-maximal concentration (IC_{50}) of 220.4 ± 0.41 µg/ml, while this extract also confirmed the highest free radical scavenging activity with an IC_{50} value of 34.18 ± 5.57 µg/ml (Atiq-ur-Rehman *et al*., 2019). Satpute *et al*., (2012), significantly explained total polyphenols were restrained in *F. arabica* representing its prospective role as a potent antioxidant. The antioxidant action was assessed by using DPPH and FRAP assay. *F. arabica* reduced the ABTS•+ radicals suggestively, representing its antioxidant activity (Satpute *et al*., 2012). Many vascular issues can be caused by oxidative stress, which indicated as a distinction between pro-oxidant and antioxidant systems. Yet, because to *F. arabica's* considerable antioxidant potential, it has been discovered to be helpful in reducing oxidative tension (Prasad *et al*., 2007). *Fagonia cretica's* methanolic extract was touted for having significant antibacterial capabilities and for its strong free radical scavenging abilities against ROS and nitrogen species scavenging abilities. Anti-inflammatory, anti-allergic, antipyretic, anti-oxidant, astringent, and thrombolytic properties were some of the additional therapeutic effects of *Fagonia* species (Puri & Bhandari, 2014). It was also reported that using *Fagonia cretica* biomass manganese oxide MnO_2 nanoparticles, as well as to assess the potential for antifungal activity by inhibiting tyrosinase and antioxidant potential(Faisal *et al*., 2022). Synthetic manganese oxide nanoparticles' (MnO_2 NPs) have the highest DPPH free radical scavenging activity measured at 200 µg/ml was 74.5 ±0.39%.

Conclusion

The key objective of this review was to unfold the pharmacological and medicinal values of *Fagonia* species. Enormous phytochemical and pharmacological examinations have been reported to affirm the medicinal value of *Fagonia* species. Extracts prepared from these plants have been known for the presence of numerous phytochemical compounds with valuable pharmacological effects that in turn reveals the immense medicinal value of *Fagonia* species against wide range of incurable diseases. This review highlighted the usage of all plant parts of multiple species of *Fagonia* and varied green synthesized nano-formulations, which are potentially beneficial for treating various ailments. The comprehensive and comparative studies can explore therapeutic potential of *Fagonia* plants in much depth. Additional investigations, to demonstrate effective bioactive constituents from this herbal plant, is still required to develop cost-effective but capable remedies contributory towards advancement of humanity. The highly ecologically safe, *Fagonia* species were also used by researchers to generate nanoparticles to enhance *Fagonia* applications in biomedicine, pharmacokinetics, pharmaceutics, food industry and in bio-nanotechnology field. Limited data is available concerning the toxicity, clinical features of this plant, as well as the *Fagonia* mediated nanoparticles and phytochemicals still need further investigation and analysis, for using this plant in treatment of various ailments.

The information from this review will help future research initiatives to develop new medicinal plant-based or phytocompound-based medications for treating various diseases or continue any clinical studies to demonstrate the efficacy of *Fagonia* medicinal plant. This review is based on an evidence-based analysis of the use of the *Fagonia* medicinal plant in treating a variety of diseases. In future this review study may be serve as a significant source of knowledge about natural medicines that will serve as therapeutic agents and may be helpful in inhibition and diagnosis of various diseases.

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