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Therapeutic Potential of Ziziphus Spina-Christi (Sidr) Extracts: Linking Green Extraction and Analytical Standardization to Pharmacological Activity and Nanodelivery

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Abstract

Ziziphus spina-christi (L.) Desf. (Sidr or Christ's thorn jujube) is a multipurpose tree of the family Rhamnaceae that has been a mainstay in Middle Eastern and African folk medicine for centuries. Leaves, bark, fruits and roots are rich in bioactive metabolites, including flavonoids, saponins, cyclopeptide alkaloids and tannins which together are responsible for a wide spectrum of pharmacological effects. There is increasing evidence that supports the medicinal promise of the crude extract but converting this research into standardised clinically relevant formulations remains a major challenge. This review, including literature published until early 2025, critically reviews the phytochemistry, green extraction strategies, as well as analytical standardisation approaches adopted for Z. spina-christi extracts, while simultaneously charting their documented pharmacological activities including antioxidant, antimicrobial, antidiabetic, hepatoprotective, anti-inflammatory, and anticancer effects. Furthermore, we discuss the rapidly emerging area of nanodelivery platforms, from green-synthesized metallic nanoparticles to polymeric and lipid-based nanocarriers, to address the inherent bioavailability problems of phytoconstituents. Special attention is paid to the way the integration of green chemistry concepts with rigorous chromatographic and spectroscopic quality control might close the gap between ethnobotanical tradition and evidence-based phytotherapy. It points out the current gaps of knowledge and directions for future study, highlighting the need for harmonised extraction techniques, verified analytical markers and well-designed clinical studies.

➢ *Highlights*

- Comprehensive survey of Ziziphus spina-christi phytochemistry covering flavonoids, saponins, cyclopeptide alkaloids, and phenolic acids across different plant organs.
- Critical evaluation of green extraction techniques (UAE, MAE, SFE, and deep eutectic solvents) with emphasis on solvent selection and process optimization.
- Integration of HPLC-DAD, LC-MS/MS, and GC-MS analytical platforms for chemical fingerprinting and marker-based standardization.
- Consolidated evidence on pharmacological activities spanning antioxidant, antimicrobial, antidiabetic, hepatoprotective, anti-inflammatory, and anticancer domains.
- Detailed discussion of nanodelivery strategies, including green-synthesized Ag, Au, ZnO, and CuO nanoparticles, plus polymeric and lipid nanocarriers that enhance bioavailability.

Keywords: *Ziziphus Spina-Christi; Sidr; Green Extraction; Phytochemistry; Analytical Standardization; HPLC; Pharmacological Activity; Nanoparticles; Nanodelivery; Green Synthesis; Antioxidant; Antimicrobial; Antidiabetic.*

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I. INTRODUCTION

For thousands of years, medicinal plants have been a primary source of therapeutic medicines, and despite spectacular breakthroughs in synthetic pharmaceutical chemistry, plant-derived natural molecules remain inspirational in modern drug discovery pipelines [1]. Ziziphus spina-christi (L.) Desf., Sidr, Nabq or Christ's thorn jujube, occupies a distinctive place among the rich variety of species recorded in the ethnobotanical pharmacopoeias of the Middle East and North Africa. The plant is in the family Rhamnaceae and is common in arid and semi-arid areas from the Sahel to the Arabian Peninsula and the Indian subcontinent [2]. In these regions, almost all the tree's organs (leaves, bark, fruits, seeds, and roots) have been used for traditional healing of maladies such as skin infections, gastrointestinal complaints, diabetes, and liver disorders [3,4].

Z. spina-christi is known for the diversity of its phytochemical repertoire. Flavonoid glycosides (rutin) and derivatives of quercetin, dammarane-type saponins (e.g. christinin-A), cyclopeptide alkaloids and a range of phenolic acids have been extracted and more or less related to the pharmacological profile of the plant [5,6]. Preclinical studies have shown promising antioxidant, antibacterial, antidiabetic, anti-inflammatory, hepatoprotective and anticancer effects, which has naturally generated interest in translating these findings to clinical applications [7,8]. However, a major bottleneck remains in that the lack of universally approved and analytically confirmed standardisation techniques makes batch-to-batch reproducibility problematic and hinders regulatory approval. The problem is aggravated by the fact that many of the published studies still depend on traditional maceration using organic solvents and pay little attention to greener options. Thus, the present review aims to fill these gaps by (i) reviewing the botanical and ethnopharmacological background of Z. spina-christi; (ii) critically analysing its phytochemical profile; (iii) assessing green extraction methods and analytical standardisation approaches; (iv) compiling evidence on pharmacological activities; and (v) discussing the emerging role of nanodelivery platforms to improve bioavailability. By tying these strands together we seek to give a road map for the shift from ethnobotanical tradition to evidence-based phytotherapy.

II. BOTANICAL DESCRIPTION AND TAXONOMIC CLASSIFICATION

Ziziphus spina-christi is an evergreen to semi-deciduous tree up to 20 m high, with a trunk diameter sometimes exceeding 60 cm in well-developed individuals [2]. The bark is light grey, deeply fissured and scaly. The crown is broad and dense, providing considerable shade in otherwise exposed habitats. The shoots are generally pale, flexible and somewhat drooping, while the thorns are paired, one straight and the other recurved, which is a morphological trait that facilitates identification in the field [9]. Leaves simple, alternating, oblong to elliptic, 2–7 cm long, with three to five prominent basal veins. The flowers are small, greenish yellow and borne in axillary cymes, while the fruit is a globose drupe, about 1-1.5 cm in diameter, turning from green to yellowish-brown on maturity [10]. Taxonomically the species is placed in the order Rosales, family Rhamnaceae and genus Ziziphus. Older literature is rich in synonyms such as Zizyphus spina-christi and Rhamnus spina-christi which may cause confusion in literature surveys [11]. It is native to North and East Africa, the eastern Mediterranean, the Arabian Peninsula and extends eastward into Iran and Pakistan, though it has been introduced to parts of tropical America and Australia [2]. This tree is adapted to semi-arid climates and is particularly drought-tolerant, and it is commonly found in wadi beds, riverbanks and disturbed sites, characteristics that confer ecological importance and agricultural accessibility for local communities.

III. ETHNOBOTANICAL AND TRADITIONAL USES

The traditional medical uses of Z. spina-christi are surprisingly broad and firmly embedded in the cultural fabric of Middle Eastern, North African and Horn of African cultures. In the Sudanese traditional medicine, leaf decoctions are used orally for treatment of digestive disorders, fever and urinary tract infections, while leaf poultices are externally applied to cure wounds, boils and skin diseases [12]. The leaves are likewise used by the Egyptian and Saudi Arabian doctors for their reputed anti-inflammatory and antipyretic effects while the fruits are eaten both as a food and as a treatment for pulmonary ailments [3,13]. In Iraq and Iran, the leaves are infused and used as a common home remedy for diarrhoea and stomach discomfort, while the bark is used to ease toothache [14]. In addition to its medical uses, the plant is also of cultural and religious importance. Sidr leaves are used in ritual washing (Ghusl) of the deceased in Islamic tradition. References to the plant (Sidrat al-Muntaha) are found in the Quran [15]. The fruits are consumed fresh or dried and are considered a nutritional resource in food-insecure areas. The wood is used as fuel and for construction purposes and the blooms as a source of food for honeybees, resulting in the much-desired Sidr honey [16]. Such multifunctionality underlines the need for sustainable harvesting procedures especially with the increasing demand for standardised extracts.

Table 1 Summary of Traditional Medicinal Uses of Z. Spina-Christi Across Different Regions

Region	Plant Part	Traditional Use	Reference
Sudan	Leaves	Oral decoction for digestive disorders, fever; external poultice for wounds and boils	[3,12]
Egypt	Fruits, Leaves	Antipyretic, anti-inflammatory; pulmonary complaints; nutritional food	[13,48]
Saudi Arabia	Leaves, Bark	Anti-inflammatory; wound healing; antimicrobial rinse; antidiabetic	[7,15]
Iraq / Iran	Leaves, Bark	Leaf infusion for diarrhoea, stomach ache; bark for toothache	[14,18]
Palestine / Jordan	Leaves	Ritual washing (Ghusl); skin infections; general tonic	[15,38]
Horn of Africa	Roots, Bark	Malaria treatment; intestinal parasites; antimicrobial applications	[12,39]
General Islamic	Leaves	Ritual purification of the deceased; Sidr honey production from flowers	[15,16]

IV. PHYTOCHEMICAL COMPOSITION

One of the most striking characteristics of Z. spina-christi is its chemical variety, with more than 100 distinct metabolites discovered so far in different plant sections. The major classes are flavonoids, triterpenoid saponins, cyclopeptide alkaloids, phenolic acids, tannins, sterols and essential oil compounds [5,6,17]. Their relative proportions vary widely depending on the plant organ, geographical origin, season of collection and extraction solvent used, which has crucial consequences for standardisation.

- *Flavonoids and Phenolic Acids*

Flavonoids are probably the most studied group of chemicals in Sidr extracts. The major flavonoid glycoside is dependably rutin (quercetin-3-O-rutinoside), especially in extracts from leaf and stem. Ghafoor et al. [18] have reported the highest amounts of rutin in methanolic stem extracts analysed by RP-HPLC to be 325 mg/100 g, but the same group observed a much lower value of 15.88 mg/100 g in the fruits. Quercetin, apigenin, kaempferol and luteolin-7-O-glucoside were also detected, as well as phenolic acids such as chlorogenic acid, p-coumaric acid, ferulic acid, syringic acid and p-hydroxybenzoic acid [18,19]. More recently, flavonoid glycosides such as quercetin-3-O-robinobioside and quercetin-3-O-β-D-xylosyl-(1→2)-α-L-rhamnoside have been extracted and their structures characterised from leaf tissues [20]. The polyphenol richness is directly responsible for the large radical-scavenging capacity reported in many in vitro experiments.

- *Saponins and Triterpenoids*

Another set of hallmark is dammarane-type triterpenoid saponins. Christinin-A, first isolated from Z. spina-christi leaves, has drawn particular attention, due to its reported hypoglycaemic action and its proposal as a chemical marker for quality assessment [21]. Other jujubogenin and ceanothic acid series of saponins have also been reported [22]. The saponin proportion is highly variable among accessions that may be ascribed to ecotypic differentiation or changes in soil chemistry over the large distribution area of the plant.

- *Alkaloids and Other Constituents*

Cyclopeptide alkaloids are macrocyclic peptides with an ether bridge which constitute a chemotaxonomic characteristic of certain Ziziphus species. Compounds such as amphibine-H and jubanine-A have been isolated from bark and root extracts of Z. spina-christi [23]. Completing the metabolite inventory are sterols (β-sitosterol, stigmasterol), fatty acids, vitamins (especially ascorbic acid in the fruit pulp) and volatile terpenoids [24,25]. The phytochemical profiling of the root extracts, together with a recent molecular docking research, showed the existence of β-sitosteryl-3β-glucopyranoside-6′-O-palmitate, among other sterol esters, and highlighted their predicted antibacterial binding affinities [26].

Table 2 Major Phytochemical Classes Identified in Different Organs of Z. Spina-Christi

Compound Class	Representative Compounds	Plant Organ	Reference
Flavonoid glycosides	Rutin (quercetin-3-O-rutinoside), quercetin-3-O-robinobioside, quercetin-3-O-galactoside	Leaves, Stem, Fruits	[18,19,20]
Flavonoid aglycones	Quercetin, apigenin, kaempferol, luteolin	Leaves, Stem	[18,34]
Phenolic acids	Chlorogenic acid, p-coumaric acid, ferulic acid, syringic acid, p-hydroxybenzoic acid	Stem, Fruits	[18,19]
Triterpenoid saponins	Christinin-A, jujubogenin glycosides, ceanothic acid derivatives	Leaves	[21,22]
Cyclopeptide alkaloids	Amphibine-H, jubanine-A	Bark, Roots	[23]
Phytosterols	β-Sitosterol, stigmasterol, β-sitosteryl-3β-glucopyranoside-6′-O-palmitate	Roots, Leaves	[24,26]
Tannins	Condensed and hydrolysable tannins	Bark, Leaves	[5,6]
Volatile terpenoids	Monoterpenes, sesquiterpenes (in essential oil)	Leaves, Flowers	[2,5]
Vitamins / Organic acids	Ascorbic acid, malic acid, citric acid	Fruit pulp	[9,10]

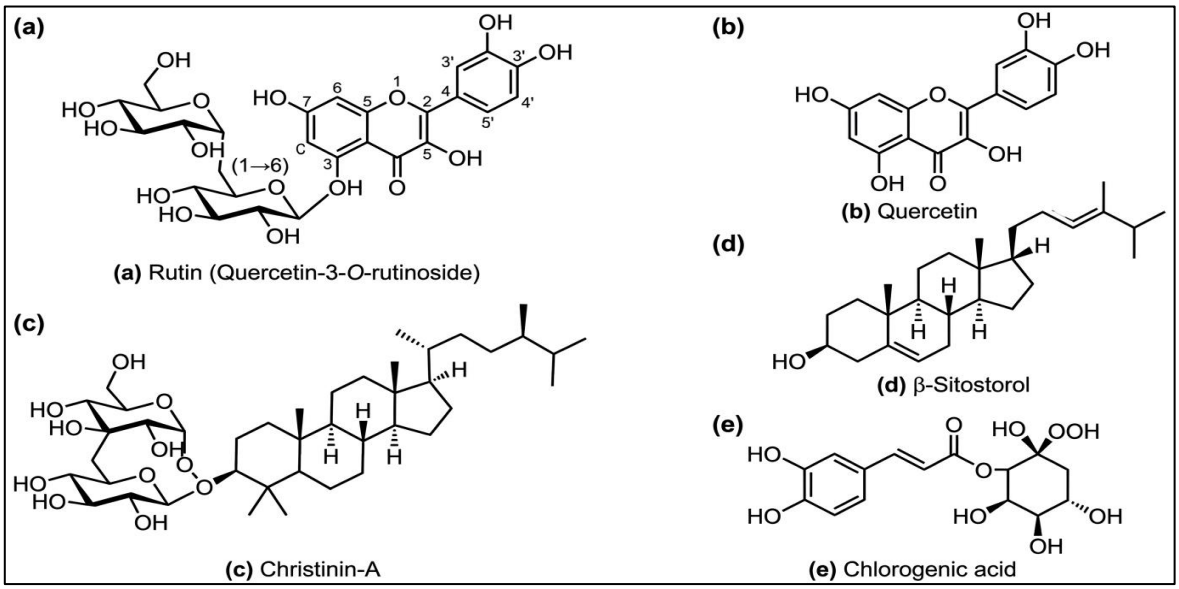

Fig 1 Chemical Structures of Selected Bioactive Metabolites Isolated from Z. Spina-Christi: (a) Rutin, (b) Quercetin, (c) Christinin-A, (d) β-Sitosterol, (e) Chlorogenic Acid.

V. GREEN EXTRACTION TECHNIQUES

The most common technique of preparation in published investigations on Z. spina-christi [27] is still the traditional approach of extracting by maceration or Soxhlet using methanol or ethanol. These techniques are simple but generally need huge amounts of solvent, extensive extraction durations and provide little selectivity. The twelve basic principles of green chemistry state that extraction procedures should be designed to minimise waste, energy consumption, and the use of renewable or benign solvents [28]. Sidr extracts have been the subject of some greener alternatives, but the literature is somewhat limited compared to that of more commercially renowned botanicals such as Camellia sinensis or Curcuma longa.

- *Ultrasound-Assisted Extraction (UAE)*

UAE is used to break down cell walls in UAE, which speeds up mass transfer and reduces extraction times by 3 to 5 times compared to standard maceration [29]. There are few published reports on Z. spina-christi polyphenols optimised systematically for UAE. Other Ziziphus spp. (e.g. Z. jujuba) have shown that solvent composition, sonication power and temperature are the most important variables [30]. The method is particularly convenient for thermolabile flavonoid glycosides provided the temperature is carefully maintained below 50 °C.

- *Microwave-Assisted Extraction (MAE)*

MAE provides fast internal heating, which speeds up the breakdown of secondary metabolites. Preliminary studies on phenolic-rich matrices with structural similarity indicate that MAE at moderate power (200–400 W) can provide equivalent or higher yields than extended

maceration in minutes instead of hours [31]. MAE may be useful for saponin-rich fractions of Z. spina-christi, since dielectric heating efficiently penetrates waxy cuticle of leaves, although care must be taken to avoid thermal breakdown of labile glycosidic linkages.

➢ *Deep Eutectic Solvents (DES) and Natural DES (NADES)*

DES and NADES are a really fascinating new solvent invention. These systems, relying on hydrogen bond donor/acceptor combinations such as choline chloride–citric acid or betaine–urea, are non-flammable, biodegradable and often dissolve polyphenols better than aqueous ethanol [32]. Their use in Ziziphus species remains mostly unknown and provides a significant opportunity for further exploration.

➢ *Supercritical Fluid Extraction (SFE)*

Supercritical CO2 extraction is a well-established technique for non-polar and moderately polar analytes. The addition of polar co-solvents (e.g., 5-15% ethanol) allows SFE to extract flavonoid aglycones and terpenoids with great selectivity and without organic solvent residues [33]. As far as we know, no specific SFE investigation on Z. spina-christi has been reported. However, the technique seems promising to generate enriched sterol and terpenoid fractions.

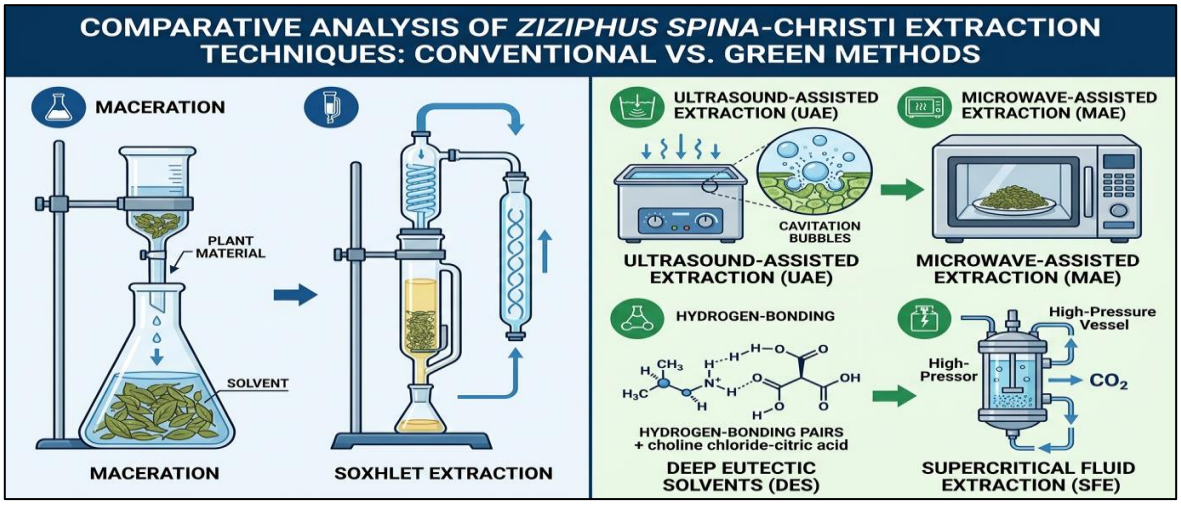

Fig 2 Comparative Schematic of Conventional Versus Green Extraction Techniques Applicable to Z. Spina-Christi: Maceration, UAE, MAE, DES-Based Extraction, and SFE.

VI. ANALYTICAL STANDARDIZATION AND QUALITY CONTROL

One of the major issues in phytomedicine research is to guarantee that the extract analysed in a given pharmacological investigation is chemically identical to what another laboratory or a manufacturing facility would produce. For Z. spina-christi, standardisation has been mainly focused on two analytical methods: chromatographic measurement of marker compounds and metabolomic fingerprinting.

➢ *HPLC-Based Marker Quantification*

Reversed-phase HPLC with UV–DAD detection has been the workhorse for the phenolic profiling of Sidr extracts. Ghafoor et al. [18] quantified rutin, quercetin, apigenin and certain phenolic acids in methanolic extracts of stem and fruit using a C18 column (250 × 4.6 mm, 5 µm) with detection at 280 nm. Later, a study standardised a leaf extract by its christinin-A level by HPLC with a detection limit of 9.45 mg/mL [21]. Recently, Hasnah et al. [34] standardised Z. spina-christi methanolic leaf extract using RP-HPLC using rutin and quercetin as dual markers and confirming concentrations of 24 ± 1.9 µg/mL and 1.4 ± 0.2 µg/mL, respectively. These findings together demonstrate that rutin, quercetin and christinin-A good basic marker panel for leaf preparations constitutes, however there is no consensus on tested methods.

➢ *LC-MS/MS and GC-MS Profiling*

Hyphenated mass spectrometric methods provide far higher sensitivity and structural discrimination. LC-ESI-Q-ToF-MS was used for phenolic-rich plant matrices similar to Z. spina-christi [35] and allowed the preliminary identification of minor glycosides and acylated derivatives not detectable by UV. GC-MS after derivatisation is more appropriate for the volatile and semi-volatile fraction comprising fatty acid methyl esters and phytosterols[36]. The ideal quality-control framework would combine HPLC-DAD quantification of main markers with LC-MS fingerprinting to capture both quantitative and qualitative batch variation.

➢ *Spectroscopic and Chemometric Approaches*

The combination of FT-IR and UV–Vis. spectroscopy together with multivariate analysis (PCA, PLS-DA) has emerged as a speedy and cost-effective approach for the authentication of herbal raw materials [37]. Mid-IR spectral fingerprinting applied to powdered Sidr leaves might in principle discern between geographic origins, or detect adulteration with cheaper Ziziphus species. However, this particular use remains to be tested for Z. spina-christi and would be a valuable contribution to the area.

Table 3. Analytical Methods Reported for Standardization of Z. Spina-Christi Extracts

Method	Target Analytes	Key Conditions	LOD / LOQ	Reference
RP-HPLC-UV	Rutin, quercetin, apigenin, chlorogenic acid, p-coumaric acid, ferulic acid	C18 (250×4.6 mm, 5 μm); UV 280 nm; MeOH gradient	Not reported	[18]
RP-HPLC-UV	Christinin-A (saponin marker)	C18; UV detection; EtOH 70% extract	9.45 mg/mL	[21]
RP-HPLC-DAD	Rutin, quercetin (dual marker standardization)	C18; DAD 280 nm; MeOH leaf extract (0.5 mg/mL)	Rutin: 24±1.9 μg/mL Quercetin: 1.4±0.2 μg/mL	[34]
HPLC-DAD	Luteolin-7-O-glucoside, rutin, quercetin, apigenin, kaempferol	Chrospher C18; DAD; comparative Ziziphus spp.	Not reported	[19]
LC-ESI-Q-ToF-MS	Phenolics, minor glycosides, acylated derivatives	High-resolution MS; ESI^-; structural elucidation	Sub-ppm mass accuracy	[35]
GC-MS	Fatty acid methyl esters, phytosterols, volatile terpenoids	Derivatization; EI-MS; HP-5ms column	Compound-specific	[36]
FT-IR + Chemometrics	Whole-extract fingerprint; authentication / adulteration screening	Mid-IR; PCA / PLS-DA multivariate analysis	N/A (qualitative)	[37]
UV-Vis spectroscopy	Total phenolics (Folin–Ciocalteu); total flavonoids ($AlCl_3$)	Spectrophotometric assays; GAE / QE quantification	N/A	[7,19]

VII. PHARMACOLOGICAL ACTIVITIES

There is a considerable amount of preclinical evidence supporting the multi-target pharmacological profile of Z. spina-christi extracts, which spans from in vitro to in vivo and increasingly in silico investigations. The following subsections summarise the main findings by activity domain.

➢ *Antioxidant Activity*

Sidr extracts radical scavenging capacity has been well demonstrated and oxidative stress has been linked in the aetiology of several chronic disorders. The DPPH, ABTS, FRAP and β-carotene–linoleate tests have all been found to produce positive results using methanolic and aqueous leaf extracts [7,26,38]. This activity is highly correlated with the total phenolic and flavonoid contents with the most contribution from rutin and quercetin derivatives. Recently, Gebrehiwot et al. [26] observed low μg/mL range DPPH IC50 values for root extracts approaching ascorbic acid standards. While these observations are intriguing it should be highlighted that in vitro antioxidant assays have well-known limits in predicting in vivo redox regulation and further mechanistic investigations exploring impacts on the Nrf2/Keap1 pathway or mitochondrial ROS generation would be instructive.

➢ *Antimicrobial Activity*

Extracts of leaf, bark and root have shown broad-spectrum antibacterial and antifungal activities against Gram positive (Staphylococcus aureus, Bacillus subtilis) and Gram negative (Escherichia coli, Pseudomonas aeruginosa) organisms [26,39]. Importantly, the silver nanoparticles synthesised from Z. spina-christi extract showed higher inhibitory zones than chloramphenicol against some tested pathogens [40]. Expanding the range of possible applications, the antifungal activity against Candida albicans (24.50 ± 1.50 mm inhibitory zone for silver-cored nanosuspensions) [41] and against the phytopathogenic fungus Fusarium oxysporum in both in vitro and in vivo pepper wilt models [42] . The synergistic enhancement of conventional antibiotics (up to 150% improvement for erythromycin) when used in combination with Sidr-derived nanoparticles indicates a possible route for combating antimicrobial resistance [41].

➢ *Antidiabetic Activity*

The hypoglycaemic activity of Z. spina-christi was initially reported in alloxan and streptozotocin induced diabetic rat models. The butanol fraction of the ethanolic leaf extract considerably lowered blood glucose levels as shown by Michel et al. [43], which was mainly ascribed to the saponin christinin-A. The seasonal variation affected saponin content and bioactivity, showing that the harvest period should be standardised [43]. In vitro α-glucosidase inhibition assays have corroborated these findings [44], implicating both flavonoids and saponins in the enzyme-inhibitory mechanism. More recent work has suggested that the anti-hyperglycaemic effect may also involve insulin-sensitizing pathways, though detailed molecular evidence is still pending.

➢ *Anti-Inflammatory and Analgesic Activity*

Several in vivo studies using carrageenan-induced paw oedema and acetic acid-induced writhing models have reported statistically significant anti-inflammatory and analgesic effects for Sidr extracts [4,45]. The mechanism appears to involve suppression of pro-inflammatory cytokines (TNF-α, IL-6) and inhibition of the COX-2/NF-κB signalling axis, consistent with the known pharmacology of quercetin and rutin [46]. Green-

synthesized silver nanoparticles prepared with Z. spina-christi leaf extract also showed anti-inflammatory activity comparable to that of indomethacin in a comparative study, while additionally exhibiting catalytic dye-degradation properties [47]. Such dual-function polymers could find fascinating uses in biomedical device coatings.

- *Hepatoprotective Activity*

Z. spina-christi hepatoprotective activities have been tested against several hepatotoxicants. Yossef et al. [48] reported that the fruit extract greatly reduced carbon tetrachloride-induced hepatotoxicity in rats as evidenced by decreased serum ALT and AST levels and improved liver histology. Another study demonstrated protection against aflatoxin B1-initiated hepatic carcinogenicity where the extract altered oxidative stress indicators and restored antioxidant enzyme activity [49]. Mechanistically, this could be explained by the quantity of flavonoids and polyphenols with the ability to chelate iron and scavenge lipid peroxyl radicals. However, pathway level studies such as Nrf2 activation and CYP450 regulation would add strength to the evidence basis.

- *Anticancer Activity*

The increasing interest in anticancer drugs from plants has resulted in assessing the cytotoxicity of Z. spina-christi against several human cancer cell lines. Farmani et al. [50] reported leaf extracts. induced apoptosis in MCF-7 breast cancer cells, with flow cytometry confirming increased sub-G1 populations. In a more exhaustive panel research, the diethyl ether fraction of stem bark extract exhibited the maximum cytotoxicity with IC50 values of 7.14, 11.2, and 11.6 µg/mL against HepG-2, A-549, and CACO-2 cell lines, respectively [51]. In the recent study by Hasnah et al. [34], it was shown that the methanolic leaf extract suppresses the proliferation and migration of HER2-positive breast cancer cell lines (ZR-75-1 and SK-BR-3) by the deregulation of p38 MAPK signalling pathway with the alteration of Bax/Bcl-2 ratios and NF-κB suppression. While these in vitro findings are compelling, the selectivity index (SI = IC50 normal/IC50 cancer) has not been systematically evaluated across studies, and in vivo tumour model data remain scarce.

Table 4 Summary of Pharmacological Activities Reported for Z. Spina-Christi Extracts and Fractions

Activity	Extract / Fraction	Model System	Key Findings	Reference
Antioxidant	MeOH root extract	DPPH, ABTS in vitro	IC_{50} in low µg/mL range, comparable to ascorbic acid; strong radical scavenging	[26]
Antioxidant	Aqueous fruit extract	DPPH, β-carotene–linoleate	Significant scavenging correlated with total phenolic content	[7]
Antimicrobial	AgNPs (leaf extract)	Disc diffusion; MIC	Zones exceeding chloramphenicol against S. aureus, E. coli; wound healing in rat model	[40]
Antimicrobial	Ag nanosuspension	C. albicans, E. coli, S. aureus	24.50±1.50 mm zone (C. albicans); 150% erythromycin enhancement	[41]
Antimicrobial	AgNPs (leaf extract)	F. oxysporum (in vitro + in vivo)	Significant reduction of pepper wilt disease in pot experiments	[42]
Antidiabetic	Butanol fraction (leaves)	Alloxan-diabetic rats	Significant blood glucose reduction; christinin-A identified as active compound	[21,43]
Antidiabetic	Leaf extracts (multi-spp.)	α-Glucosidase inhibition in vitro	Dose-dependent enzyme inhibition; flavonoids and saponins implicated	[44]
Anti-inflammatory	MeOH leaf extract	Carrageenan paw oedema	Significant oedema reduction; TNF-α, IL-6 suppression; COX-2/NF-κB pathway	[4,45,46]
Anti-inflammatory	Green-synthesized AgNPs	Comparative study vs indomethacin	Comparable anti-inflammatory activity; dual catalytic dye-degradation	[47]
Hepatoprotective	Aqueous fruit extract	CCl_4-induced hepatotoxicity (rats)	Reduced ALT, AST; improved histopathology; restored antioxidant enzymes	[48]
Hepatoprotective	Leaf/fruit extract	Aflatoxin B_1 model (rats)	Protection against AFB_1-initiated hepatic carcinogenicity	[49]
Anticancer	MeOH leaf extract	MCF-7 (breast cancer)	Apoptosis induction; increased sub-G_1 population by flow cytometry	[50]
Anticancer	Diethyl ether fraction (bark)	HepG-2, A-549, CACO-2 panel	IC_{50}: 7.14 (HepG-2), 11.2 (A-549), 11.6 (CACO-2) µg/mL	[51]
Anticancer	MeOH leaf extract	ZR-75-1, SK-BR-3 (HER2+)	Inhibited proliferation/migration via p38 MAPK; Bax/Bcl-2 modulation; NF-κB suppression	[34]

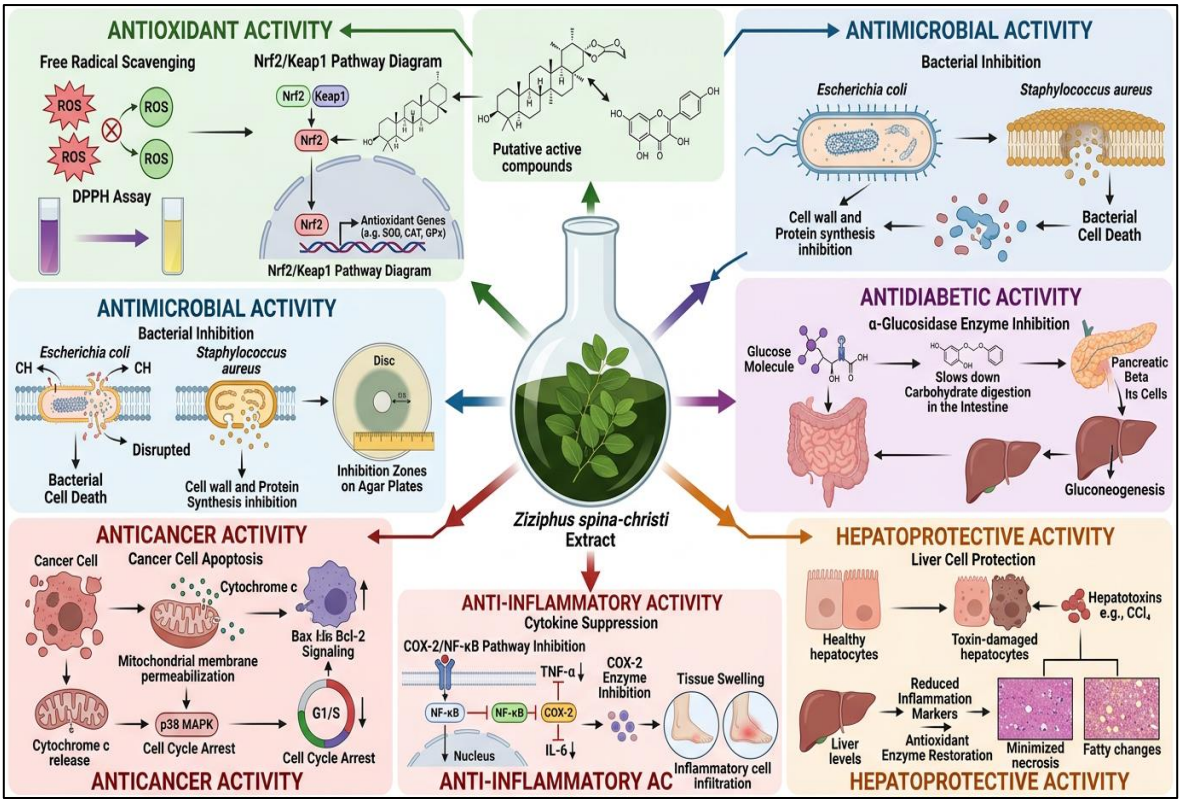

Fig 3 Illustrative Summary of the Multi-Target Pharmacological Activities of Z. Spina-Christi Extracts and their Proposed Molecular Mechanisms.

VIII. NANODELIVERY STRATEGIES

Many phytoconstituents of Z. spina-christi exhibit bioactivity, however they have poor water solubility, low gastrointestinal absorption, and quick first-pass metabolism, all of which reduce oral bioavailability [52]. Nanotechnology-based delivery platforms provide a plethora of alternatives including augmentation of solubilisation, controlled release and targeted tissue accumulation. In the field of Sidr phytochemicals, two main types of nanodelivery have been investigated: green-synthesized metallic nanoparticles and organic nanocarriers.

➢ *Green-Synthesized Metallic Nanoparticles*

The green synthesis of silver nanoparticles (AgNPs) by Z. spina-christi aqueous leaf or fruit extract is the most described nanomaterial platform. In this method phenolic and flavonoid chemicals function as reducing agents (Ag^+ to Ag^0) and capping/stabilizing agents controlling the particle development and preventing their aggregation [40] at the same time. Recently, Al-Rajhi et al. [40] reported spherical, non-aggregated AgNPs with a hydrodynamic diameter of ~111 nm, a polydispersity index of 0.38 and a zeta potential of −27 mV, showing reasonable colloidal stability. These nanoparticles showed higher antibacterial activity than chloramphenicol and when prepared as a topical lotion, it considerably promoted wound closure and granulation tissue formation in a rat model without observable toxicity.

The biosynthesis of zinc oxide nanoparticles (ZnO-NPs) utilising Sidr leaf extract was also characterised. Shnawa et al. [53] discovered ZnO-NPs with a size of around 38 nm in the hexagonal wurtzite phase showing both antibacterial and antioxidant capabilities. In a more complex formulation, a trimetallic CuO/Ag/ZnO nanocomposite was prepared by Ibrahim et al. [54] using Z. spina-christi extract, optimised with a central composite design (CCD) and displayed a synergistic antimicrobial effect owing to the combined release of Cu^{2+}, Ag^+ and Zn^{2+} ions. The environmental remediation capability of these materials has been demonstrated by further studies on the adsorptive removal of crystal violet dye by Cu-NPs prepared from fruit extract [55].

However, the preparation of gold nanoparticles (AuNPs) is less common by Sidr extracts yet they are an attractive prospect because to their uses in photothermal therapy and bioimaging. The surface plasmon resonance characteristics of AuNPs can be adjusted by altering the extract concentration and reaction temperature but specific optimisation studies for Z. spina-christi are currently lacking.

➢ *Polymeric and Lipid-Based Nanocarriers*

Metallic nanoparticles possess intrinsic antimicrobial properties, but polymeric nanoparticles (e.g. PLGA, chitosan-based systems) and lipid nanocarriers (solid lipid nanoparticles, nanostructured lipid carriers, liposomes) are more suitable for the encapsulation and delivery of specific phytochemical fractions or purified compounds such as rutin or christinin-A [56]. Chitosan nanoparticles are of particular interest for the oral delivery of polyphenols due to their mucoadhesive properties and their ability to protect labile molecules from gastric degradation [57]. Another possible means to improve the oral absorption of lipophilic terpenoids from Z. spina-

christi is self-nanoemulsifying drug delivery systems (SNEDDS), however published formulation research are limited thus far to structurally comparable plant systems. The use of computational methods (molecular dynamics, QSPR modelling) for predicting nanocarrier–phytochemicals compatibility could speed formulation development.

Table 5 Green-Synthesized Nanoparticles from Z. Spina-Christi: Synthesis Parameters, Characterization, and Biological Activities

NP Type	Plant Part	Size / Morphology	Zeta (mV)	Biological Application	Reference
AgNPs	Leaf extract	~111 nm; spherical; PDI 0.38	−27.0	Antibacterial (> chloramphenicol); wound healing cream in rats	[40]
Ag nano-suspension	Leaf extract	~34 nm; spherical	Not reported	MDR antimicrobial; C. albicans (24.5 mm zone); erythromycin synergy (150%)	[41]
AgNPs	Leaf extract	Variable; stabilised by polyphenols	Negative	Antifungal (F. oxysporum); pepper wilt disease control in vivo	[42]
ZnO-NPs	Leaf extract	~38 nm; hexagonal wurtzite	Not reported	Antimicrobial + antioxidant activity	[53]
CuO/Ag/ZnO trimetallic	Plant extract	CCD-optimised; composite	Not reported	Synergistic antimicrobial via multi-ion release (Cu^{2+}, Ag^{+}, Zn^{2+})	[54]
Cu-NPs	Fruit extract	Nanoscale; characterised by XRD, TEM, FESEM	Not reported	Crystal violet dye adsorption; antibacterial assay	[55]
AgNPs	Leaf extract	Characterised by UV-Vis, FT-IR, SEM, XRD, TGA	Not reported	Anti-inflammatory (comparable to indomethacin); catalytic dye degradation	[47]

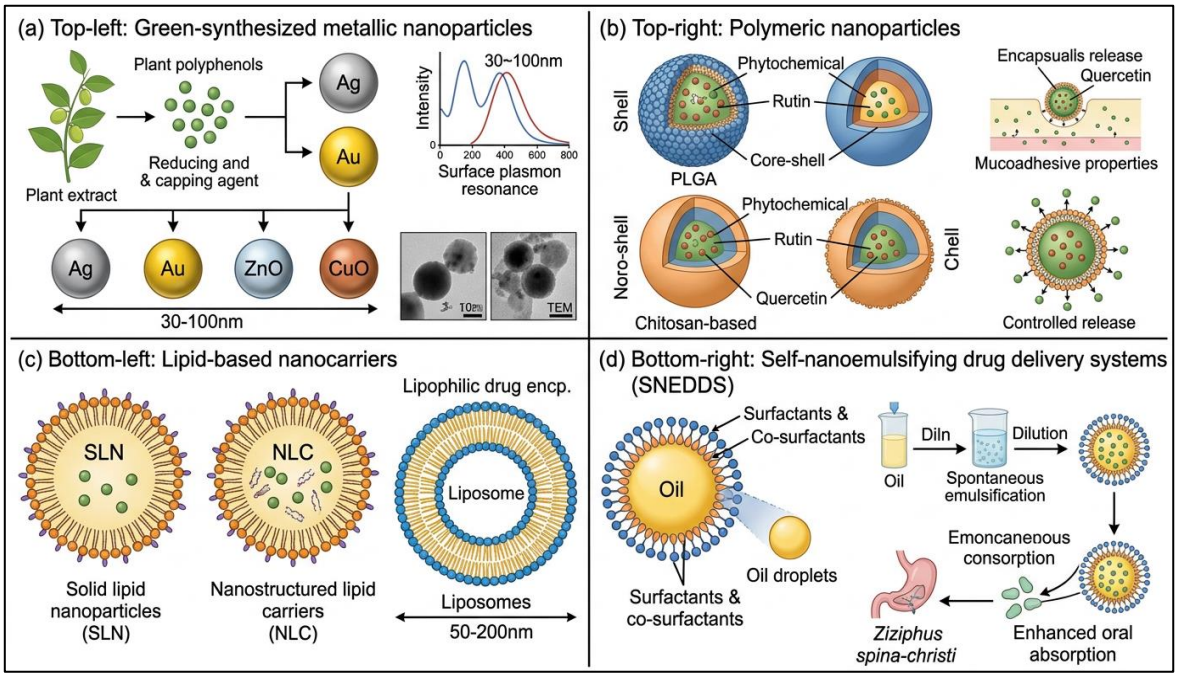

Fig 4 Overview of Nanodelivery Platforms Explored for Z. Spina-Christi Bioactives: (a) Green-Synthesized Metallic NPs, (b) Polymeric Nanoparticles, (c) Lipid-Based Nanocarriers, (d) Self-Nanoemulsifying Systems.

IX. TOXICOLOGICAL PROFILE AND SAFETY CONSIDERATIONS

Few but mostly promising safety data are available for Z. spina-christi extracts. Acute oral toxicity experiments in mice showed LD50 values > 5000 mg/kg for aqueous and ethanolic leaf extracts, classifying them as practically non-toxic according to the Globally Harmonised System [58]. No significant changes in haematological parameters, liver enzyme or kidney function markers were seen in sub-chronic feeding studies (28 or 90 days) at dosages up to 500 mg/kg/day, while

some authors observed moderate, dose-dependent reductions in body weight gain [59]. In silico organ toxicity estimates for root derived phytochemicals revealed no hepatotoxicity or cytotoxicity for the main sterols and saponins [26].

The biosafety profile of the green synthesised nanoparticles is highly dependent on metal core, particle size, surface chemistry and dose. Al-Rajhi et al. [40] did not observe any histological abnormalities in rats treated with AgNP-loaded cream for 14 days. However, long-term biodistribution and possible buildup of metallic nanoparticles in organs remain outstanding issues to be addressed prior to serious consideration of clinical translation. There is no evidence at all on reproductive and developmental toxicity of nanomaterials derived from Sidr which is a crucial gap.

X. FUTURE PERSPECTIVES AND RESEARCH GAPS

Despite the large amount of research gathered in this review, certain important gaps still exist. First of all, there is a clear need for harmonised extraction techniques. Most of the published pharmacological data are derived from crude methanolic or ethanolic extracts generated under non-standardized circumstances, making comparisons across different studies risky. Simultaneously, the use of green extraction technologies (UAE, MAE, DES) with response-surface-optimized parameters will increase both repeatability and environmental sustainability.

Second, analytical standardisation should extend from single-marker HPLC to multi-marker and fingerprint-based techniques. The development of a consensus monograph, similar to the monographs issued by the European Pharmacopoeia for better known botanicals, would substantially improve quality control and regulatory acceptability. Such an initiative might be supported by LC-MS/MS based metabolomics paired with chemometric categorisation.

Third, while the preclinical results are strong for multiple pharmacological endpoints, clinical data are almost non-existent. Well-designed randomised controlled trials, even on a pilot size, are urgently needed to validate the antidiabetic, wound-healing and anti-inflammatory claims that are now based solely on animal models.

Fourth, the nanodelivery literature is expanding but is mostly limited to green-synthesized metallic nanoparticles. A reasonable and effective next step would be to design formulations systematically using biodegradable polymeric and lipid carriers for purified bioactives (e.g., rutin, christinin-A, quercetin). It is important to couple the nanocarrier design with the pharmacokinetic studies to show the improved bioavailability for the translational development.

Lastly, sustainable sourcing and farming procedures must be addressed. There is increasing economic interest in Sidr goods, partly because of the global popularity of Sidr honey, and the risk of overharvesting wild populations is not minor. Agronomic studies on culture optimisation, chemotypic selection and post-harvest handling would benefit both conservation and the supply chain for standardised phytopharmaceutical production.

XI. CONCLUSION

Ziziphus spina-christi is a phytochemically rich and pharmacologically flexible plant and deserves much greater attention from the modern phytotherapy research community than it has received so far. The confluence of many groups of bioactive metabolites including flavonoids, saponins, cyclopeptide alkaloids and phenolics forms the basis of a broad pharmacological spectrum which includes antioxidant, antibacterial, antidiabetic, anti-inflammatory, hepatoprotective and anticancer effects. Although there is a lack of extensive research on Sidr, green extraction methods provide plausible routes for more sustainable and selective recovery of phytochemicals. HPLC-based marker quantification and LC-MS fingerprinting are undergoing analytical standardisation, however there is no globally approved quality control system. Nanodelivery techniques, especially green-synthesized metallic nanoparticles have shown great potential to enhance antibacterial and wound-healing properties. However, their long-term safety and scalability is yet to be thoroughly examined. But moving from preclinical promise to clinical validation is the single biggest barrier ahead. This will necessitate concerted efforts in the optimisation of extraction, validation of analytical methods, pharmacokinetic evaluation of nanoformulations and finally human clinical trials. Systematic investigation of these gaps could pave the way for the development of standardised and evidence-based therapeutic products from Z. spina-christi, thus honouring and reviving an ancient medicinal heritage.

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