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A comprehensive review of the medicinal properties of *Terminalia arjuna* and its major constituent arjunolic acid: a natural product source for new drug leads

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Plants have long been a primary source of natural products for medicine. *Terminalia arjuna*, a deciduous tree native to the Indian subcontinent, is renowned for its diverse biological properties, such as anti-cancer, anti-diabetic, and cardioprotective effects. Various parts of this tree have been used to treat numerous ailments such as cancer, diabetes, inflammation, and microbial infections, as mentioned in ancient medicinal texts such as *Ayurveda* and *Charaka Samhita*. Arjunolic acid, a pentacyclic triterpene, is a major constituent of *T. arjuna*, and exhibits a plethora of biological properties such as anti-cancer, anti-diabetic, anti-inflammatory, and antioxidant activities. Diverse research groups have utilized arjunolic acid as a template for synthesizing various semi-synthetic derivatives, which have been evaluated for their anti-cancer, anti-diabetic, and antioxidant properties. This review comprehensively compiles and discusses the literature related to *T. arjuna*, arjunolic acid and its derivatives, focusing on their medicinal properties and the mechanism of their biological activities.

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1. Introduction

Natural products, classified into alkaloids, carbohydrates, flavonoids, lipids, steroids, terpenes, *etc.*, have been a rich and consistent source of biologically important and chemically diverse molecules.[1,2] In view of the recent surge in FDA approvals for natural-product-based drug leads,[3,4] terpenes present a promising opportunity to identify new drug candidates, as they are the largest class among natural products. The major pentacyclic triterpene constituent of *T. arjuna*, arjunolic acid, has received widespread attention from various research groups[5,6] for its diverse biological properties. The structural feasibility of arjunolic acid to undergo various semi-synthetic transformations has resulted in analogues with interesting *in vitro* and *in vivo* biological activity.[7–9] Although efforts have been made to review the literature on *T. arjuna*[10–16] and arjunolic acid,[5,6,17] the present review aims to comprehensively compile and discuss the following areas: (a) *T. arjuna* and its medicinal properties, (b) the isolation of arjunolic acid from various sources and its biological activities, and (c) various semi-synthetic derivatives of arjunolic acid, along with their biological properties and action mechanisms, reported to date.

1.1 Morphology of *Terminalia arjuna (T. arjuna)*

Terminalia arjuna is a species in the genus *Terminalia* of the family Combretaceae, which includes approximately 20 genera and 600 species.[18] The genus name *Terminalia* refers to the terminal arrangement of leaves on many species in this group. *T. arjuna* is found throughout the sub-Himalayan regions of Bihar, Delhi, Madhya Pradesh, Uttar Pradesh, and the Deccan Plateau in India, as well as in the forests of Sri Lanka, Bangladesh, Mauritius, and Myanmar.[19,20] It is a deciduous tree with buttressed roots, a sturdy trunk, and horizontally spreading branches and can reach heights of 60–70 feet (Fig. 1). The bark has a single-layered epidermis with hair-like projections, along with periderm and secondary phloem in mature bark. Its bark is usually white-grey, turning pink depending on the season and age, and it flakes off in large, flat pieces.[21]

The leaves are conical, oblong or elliptic, typically 10–15 cm long and 4–7 cm wide, with a green or dark-green upper surface and a light-brown underside. The petioles have one or two prominent glands at the top.[21,22] The flowers are pale yellow to milky white, bisexual, and grow in dense clusters at the branch tips or as axillary spikes. Each flower has 10 stamens and an ovary covered with reddish or yellow hairs, while the calyx is glabrous. The woody fruit is 2.5–3.5 cm long with five angled wings that curve upward. *T. arjuna* flowers from March to June, with fruit appearing between September and November.[21] *T. arjuna* contains many phytochemicals that have been reported to exhibit biological properties (Table 1 and Fig. 2). Among

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Fig. 1 Images of *T. arjuna*, flowers, fruits, leaves and bark.

them, arjunolic acid is the major constituent, and this compound has been the focus of diverse research groups as it was reported to exhibit a plethora of biological properties.[5,6]

Apart from the major constituent arjunolic acid, many phytochemicals, as described in Fig. 2, have been reported to exhibit biological activities. This further affirms that *T. arjuna* has been a source of bioactive molecules, and it would be interesting to explore the potential of these other phytochemicals in various drug discovery programs.

1.2 Uses of *T. arjuna* in traditional medicine

T. arjuna has been valued since the Vedic era, referred to as *Arjun* in Ayurvedic texts. It appears in ancient medicinal literature, including the *Astang Hridayam*, *Charaka Samhita*, and *Sushruta Samhita*. The Ayurvedic scholar Vagbhattacharya was the first to mention the use of bark powder prepared from its stem for heart-related ailments, a use later supported by Chakradattam and Bhavasisram. In Ayurveda, *T. arjuna* is considered a cardiotonic and is used to treat conditions such as *kshata* (wounds), *kshaya* (emaciation), *visham* (poison), *raktavikara* (styptic), *medoroga* (diabetes), *prameha* (urinary disorders), and *vrana* (ulcers). It is also known to relieve painful urination in diabetic conditions. A decoction of *T. arjuna* bark in conjunction with white sandalwood is used to boost sperm count in men and to relieve menstrual pain and leukorrhea in women. It is applied for skin ailments, fever, and general vitality enhancement.[73]

Root paste is applied to the forehead to alleviate headaches. Leaf paste mixed with milk and sugar is given to treat spermatorrhoea, while water-soaked leaves are used for dyspepsia and burning sensations. In traditional veterinary medicine, leaves combined with *Syzygium cumini* and *Acacia catechu* are used to treat cattle diarrhoea.[74,75] Healers in Tamil Nadu's Kanchipuram district use fruit paste topically for wounds and inhale boiled bark for headaches and toothache relief.[76] The Malamalasar tribe in Parambikulam uses fresh leaf juice for earache, while the powdered bark is employed for heart issues.[77] In Madhya Pradesh's Surguja district, bark is used for treating fever and hypertension. In the Malkangiri district of Orissa, fresh bark is chewed as an antacid.[78] Rajasthan communities combine bark powder with ghee and milk to improve heart health.[79]

Throughout India, pastes of the bark are applied to wounds for faster healing and to stop bleeding. The bark decoction is useful for treating asthma, dysentery, ulcers, and acne (when mixed with honey).[80] Bark ash is used to treat snakebites and scorpion stings, while a bark paste is applied to the area of a fracture for quicker recovery and to reduce swelling from injuries.[77,81] It is also employed for gleet, urinary issues, as an expectorant, aphrodisiac, tonic, and diuretic.[82]

1.3 Medicinal properties of *T. arjuna*

1.3.1 Cardioprotective activity. *T. arjuna* has been used for the treatment of heart disease since ancient times. A study on the effects of an aqueous extract of *T. arjuna* bark to understand the mechanisms involved in cardiovascular disorders was conducted, and the oleanane triterpenoids present in this extract were found to be primarily responsible for the plant's cardioprotective effects.[83] The bark decoction also significantly lowered body mass index and systolic blood pressure in angina patients without affecting normal kidney or liver function.[84] Studies showed that administering bark powder to angina patients significantly reduced the frequency of angina in both ischemic cardiomyopathy and post-myocardial infarction angina. This treatment improved the left ventricular ejection fraction. It reduced left ventricular mass, providing relief from coronary heart failure, and long-term use of the drug did not alter normal kidney or liver physiology.[85]

The herbal formulation "Lipistat," which includes the bark of the arjuna tree, reduced the loss of myocardial high-energy phosphate stores and lactate accumulation in myocardial tissue in cases of isoproterenol-induced myocardial necrosis, also offering protection in ischemic heart disease. Additionally, *T. arjuna* bark extract improved symptoms and signs in New York Heart Association (NYHA) class patients, reducing left ventricular end-diastolic and end-systolic volume indices, while increasing left ventricular ejection fractions. Long-term treatment and evaluation of NYHA class patients showed improved symptoms, signs, and exercise tolerance.[86] It was observed that the ethanolic extract of the bark reduced total cholesterol, HDL cholesterol, triglyceride levels, LDL cholesterol, and LDL/HDL ratios, without impacting renal or hepatic function.[87]

The hypolipidemic activity of *T. arjuna* was evaluated in experimentally induced atherosclerosis in rabbits fed on a cholesterol-rich diet, where it acted as a hypolipidemic agent, partially inhibiting atheroma formation and indicating an antiatherogenic role.[88] A study on "Hartone," an arjuna-based herbal formulation, found that 80% of patients receiving Hartone treatment experienced relief from stable angina

Table 1 Phytochemicals present in *T. arjuna* and their medicinal properties

Part	Phytochemicals	Medicinal properties
Stem bark	Arjunolic acid (**1**)[23,24]	Cardioprotective, anti-cancer[7,25]
	Arjunin (**2**)[23,24,26]	Anti-cancer[27]
	Arjungenin (**3**)[23,24]	Cytotoxic[28]
	Terminic acid (**4**)[29]	—
	Terminolitin (**5**)[23,24]	—
	Arjunic acid (**6**)[26]	Antioxidant[30]
	2α,3β-Dihydroxyurs-12,18-dien-28-oic acid- 28-*O*-β-D-glucopyranosyl ester (**7**)[31]	—
	2α,3β,23-Trihydroxyurs-12,18-dien-28-oic acid-28-*O*-β-D-glucopyranosyl ester (**8**)[31]	—
	Quadranoside VIII (**9**)[31]	—
	Kajiichigoside F1 (**10**)[31]	—
	2α,3β,23-Trihydroxyurs-12,19-dien-28-oic acid-28-*O*-β-D-glucopyranosyl ester (**11**)[31]	—
	Arjunetin (**12**)[23,24]	Anti-viral,[32] antioxidant[33]
	Arjunoside I (**13**), arjunoside II (**14**), arjunoside III(**15**), arjunoside IV (**16**)[34,35]	—
	Arjunolone (**17**)[36]	—
	Arjunolitin (**18**)[37]	—
	Arjunaphthanoloside (**19**)[38,39]	—
	Arjunoglycoside I (**20**), arjunoglycoside II (**21**), arjunoglycoside III (**22**), arjunoglycoside IV (**23**), arjunoglycoside V (**24**)[40,41]	—
	Olean-3β,22β-diol-12-en-28-oic acid-28-β-D-glucopyranoside (**25**)[42]	—
	Terminarjunoside I (**26**) and terminarjunoside II (**27**)[43]	—
	Terminoside A (**28**)[44]	Inhibits NO production[45]
	Terminoic acid (**29**)[44]	—
	Arjunone (**30**)[36]	—
	Luteolin (**31**)[36]	Antioxidant, antimicrobial, anticancer[46]
	Baicalein (**32**)[36]	Anticancer, antimicrobial, anti-biofilm[47]
	Ethyl gallate (**33**)[36]	
	Gallic acid (**34**)[36]	Antioxidant[48–50]
	Kempferol (**35**)[36]	Anti-cancer, anti-inflammatory[51,52]
	Oligomeric proanthocyanidin (**36**)[36]	—
	Pelargonidin (**37**)[36]	—
	Quercetin (**38**)[36]	Antimicrobial, anticancer[47]
	(+) catechin (**39**), (+) gallocatechin (**40**) and (−) epigallocatechin (**41**)[53]	Antioxidant[54]
	Gallic acid (**34**), ellagic acid (**42**)[53]	Antioxidant, hepatoprotective.[48–50]
	3-*O*-Methyl-ellagic acid-4-*O*-β-D-xylopyranoside (**43**)[53]	—
	3-*O*-Methyl ellagic acid-3-*O*-β-D-rhamnoside (**44**)[53]	—
	3-*O*-Methyl ellagic acid-4′-*O*-α-L-rhamnopyranoside (**45**)[31]	—
	(−)-Epicatechin (**46**)[31]	Antioxidant[54]
	Pyrocatechol (**47**)[55]	Antioxidant[54]
	Punicallin (**48**)[56]	Anti-cancer[57]
	Castalagin (**49**)[58]	Antibacterial, antiviral[59]
	Casuariin (**50**)[58]	Anti-cancer, antioxidant[60,61]
	Casuarinin (**51**)[58]	Anti-cancer, anti-inflammatory[60,61]
	Punicalagin (**52**)[58]	Antioxidant[57]
	Terchebulin (**53**)[58]	Antibacterial[62]
	Terflavin C (**54**)[58]	Antimicrobial[63]
	β-Sitosterol (**55**)[29]	Antimicrobial[64]
Roots	Arjunoside I–IV (**13–16**)[29]	
	Arjunolic acid (**1**)[29]	Cardioprotective, anti-cancer[7,25]
	Oleanolic acid (**56**)[29]	Antimicrobial, anti-cancer[65]
	Terminic acid (**4**)[29]	—
	2α,19α-Dihydroxy-3oxo-olean-12-en-28-oic acid −28-*O*-β-D-glucopyranoside (**57**)[66]	—

Table 1 (*Contd.*)

Part	Phytochemicals	Medicinal properties
	Arjunic acid (**6**)[23,24]	Antioxidant[30]
	Arjunetoside (3-*O*-β-D-glucopyranosyl-2α,3β,19α-trihydroxyolean-12-en-28-oic acid-28-*O*-β-D-glucopyranoside) (**58**)[67]	—
Fruits	Arjunic acid (**6**)[68]	Antioxidant[30]
	Arjunone (**30**)[68]	—
	Arachidic acid (**59**) and stearic acid (**60**)[68]	Anti-inflammatory[69]
	Cerasidin (**61**)[68]	—
	Ellagic acid (**42**)[68]	Antioxidant.[48–50]
	Friedelin (**62**)[68]	Anti-inflammatory, antibacterial[70]
	Gallic acid (**34**)[68]	Antioxidant[48–50]
	Hentriacontane (**63**)[68]	—
	Methyl oleate (**64**)[68]	—
	Myristyl oleate (**65**)[68]	—
	β-Sitosterol (**55**)[68]	Anti-inflammatory[64]
Leaves	Gallic acid (**34**)[71]	Antioxidant[48–50]
	Luteolin (**31**)[71]	Antimicrobial, anticancer.[46]
	Quercetin (**38**)[71]	Antimicrobial, anticancer[47]
	Catechin (**39**)[71]	Antioxidant[54]
	Epicatechin (**46**)[71]	Antioxidant[54]
	Apigenin (**66**)[71]	Antibacterial, anticancer[72]

pectoris compared to those on isosorbide mononitrate (ISMN), with a higher reduction in heart attack rates than ISMN. This formulation also improved blood pressure response to stress without disturbing renal or hepatic function.[89]

In rabbits, oral administration of a suspension of bark powder of *T. arjuna* for 12 weeks increased myocardial antioxidants, superoxide dismutase, catalase, and glutathione levels, while inducing heat-shock protein-72. In cases of ischemic reperfusion injury, oxidative stress and heart tissue injury were prevented in bark powder-administered rabbit hearts. In these treated rabbits, left ventricular end-diastolic pressure normalized within 10 minutes of reperfusion, and myocardial lipid peroxidation levels were lower.[90] Bark powder treatment significantly reduced total cholesterol and LDL cholesterol levels and decreased lipid peroxide levels.[91] The bark powder of *T. arjuna* reduced ischemic mitral regurgitation (IMR), improved the E/A ratio (indicating early and late phases of ventricular filling), and reduced angina frequency.[90] In acute myocardial infarction, a 500 mg oral dose of *T. arjuna* bark powder administered for three months decreased ischemic mitral regurgitation and significantly reduced angina frequency.[92]

Another study based on the hypothesis that the aqueous stem bark extract of *T. arjuna* (TAE) could inhibit IL-18-induced atherosclerosis through the NF-κB/PPAR-γ-mediated pathway in ApoE-/mice was conducted. Twelve-week-old male ApoE−/− mice, fed with a standard chow diet, were divided into four groups ($n = 6$ per group): Group I (control): Phosphate-buffered saline (PBS) for 2 months. Group II: Recombinant IL-18 (rIL-18) for 1 month, followed by PBS for 1 month. Group III: rIL-18 for 1 month, followed by TAE for 1 month. Group IV: rIL-18 for 1 month, followed by atorvastatin for 1 month. Treatment with IL-18 significantly elevated pro-inflammatory IL-18 levels (1178.66 ± 8.08 pg mL^{-1} *vs.* 170 ± 9.16 pg mL^{-1} in controls, $p < 0.001$) and downregulated the cholesterol efflux gene PPAR-γ (0.6-fold *vs.* 1.00 in control mice). Administration of TAE significantly reduced IL-18 levels (281.66 ± 9.60 pg mL^{-1} *vs.* 1178.66 ± 8.08 pg mL^{-1}) and upregulated PPAR-γ expression (1.5-fold *vs.* 0.6-fold in the IL-18-treated group). TAE also decreased atherogenic lipids and reduced the percentage of atherosclerotic lesion area, showing comparable efficacy to atorvastatin. The findings suggest that TAE mitigates IL-18-induced atherosclerosis *via* the NF-κB/PPAR-γ-mediated pathway, highlighting its potential as a therapeutic agent.[93]

Another study investigated the therapeutic and prophylactic potential of *T. arjuna* bark extract in a rat model of isoproterenol (ISO)-induced chronic heart failure (CHF). Rats were administered isoproterenol (ISO) at a dose of 85 mg kg^{-1} subcutaneously, twice at an interval of 24 hours, to induce CHF. Fifteen days post-injection, the rats exhibited reduced cardiac function, including declines in the maximal rate of rise and fall of left ventricular pressure (LV (dP/dt) max and LV (dP/dt) min), cardiac contractility index (LV (dP/dt) max/LVP), and cardiac output. Additionally, an increase in left ventricular end-diastolic pressure was observed. The CHF rats also showed significantly elevated serum levels of creatine kinase isoenzyme-MB (CK-MB) and malondialdehyde (MDA), along with reduced activities of antioxidant enzymes, such as superoxide dismutase (SOD), and reduced glutathione (GSH). Alterations in lipid profiles, elevated levels of the pro-inflammatory cytokine tumor necrosis factor-alpha (TNF-α), and histological heart damage were also evident. Treatment with *T. arjuna* bark extract (500 mg kg^{-1}, orally) both before and for 15 days after ISO administration significantly improved cardiac function and reduced

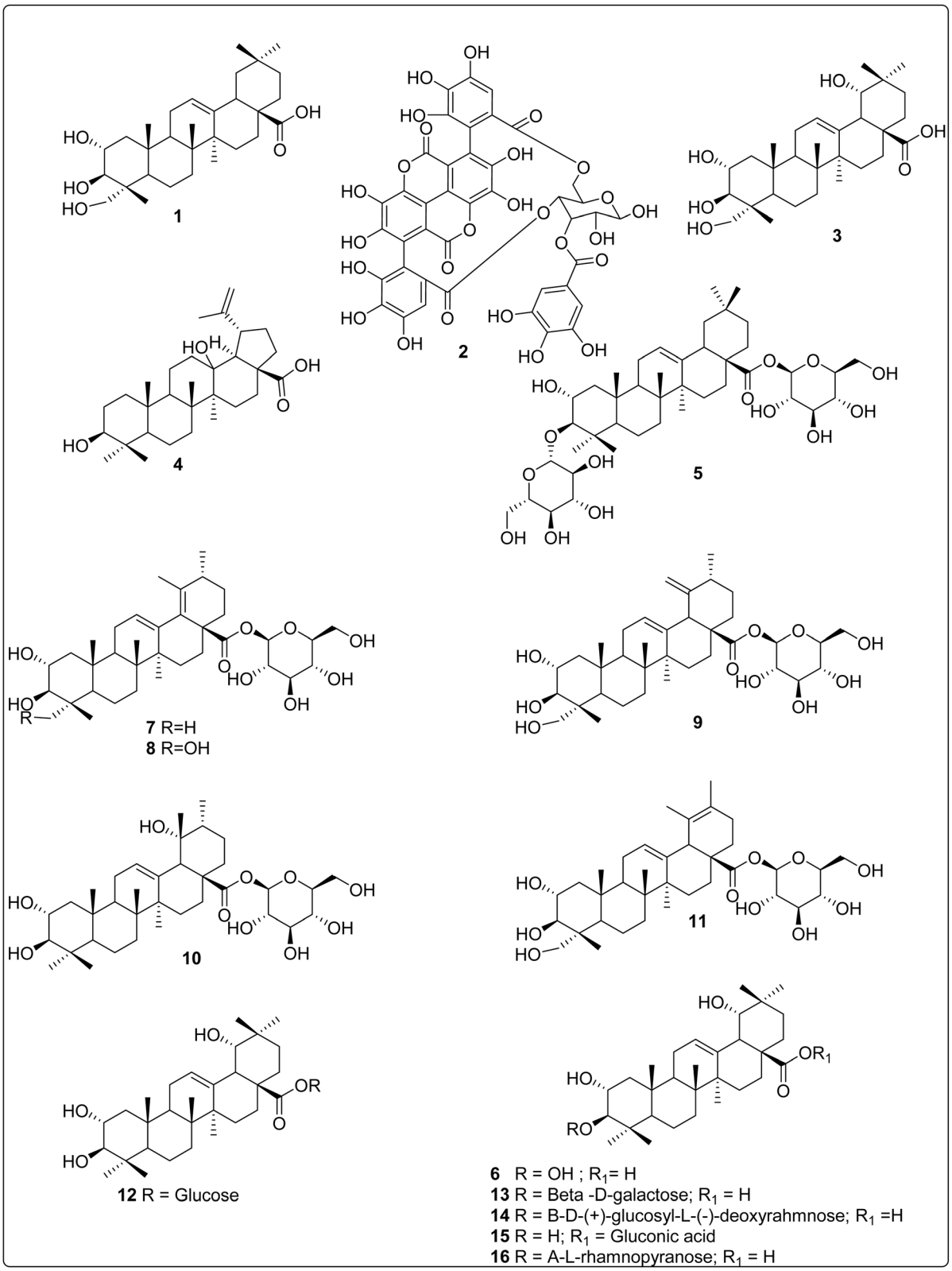


Fig. 2 Structures of various chemical constituents isolated from *T. arjuna*.

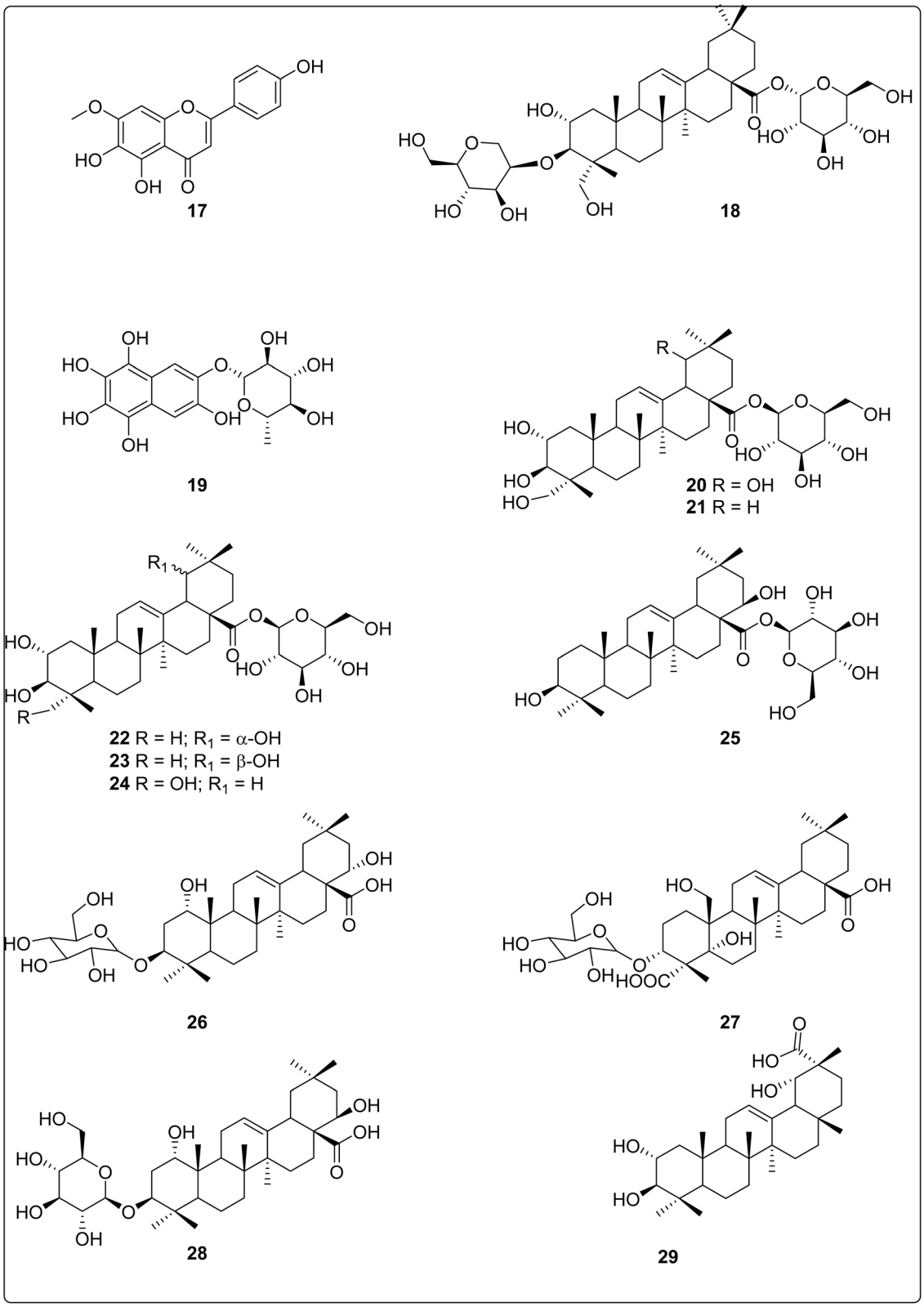
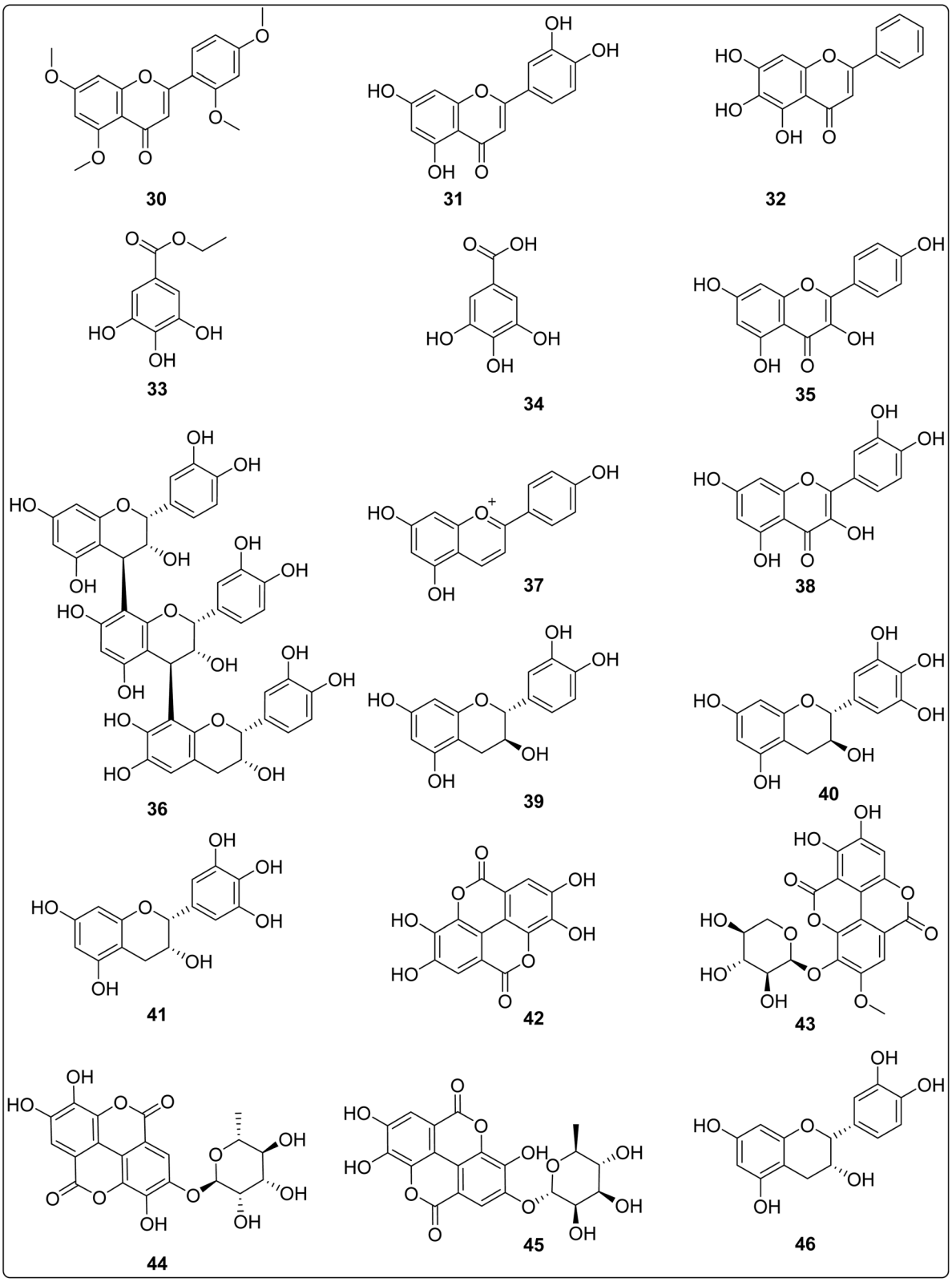


Fig. 2 (*Contd.*)



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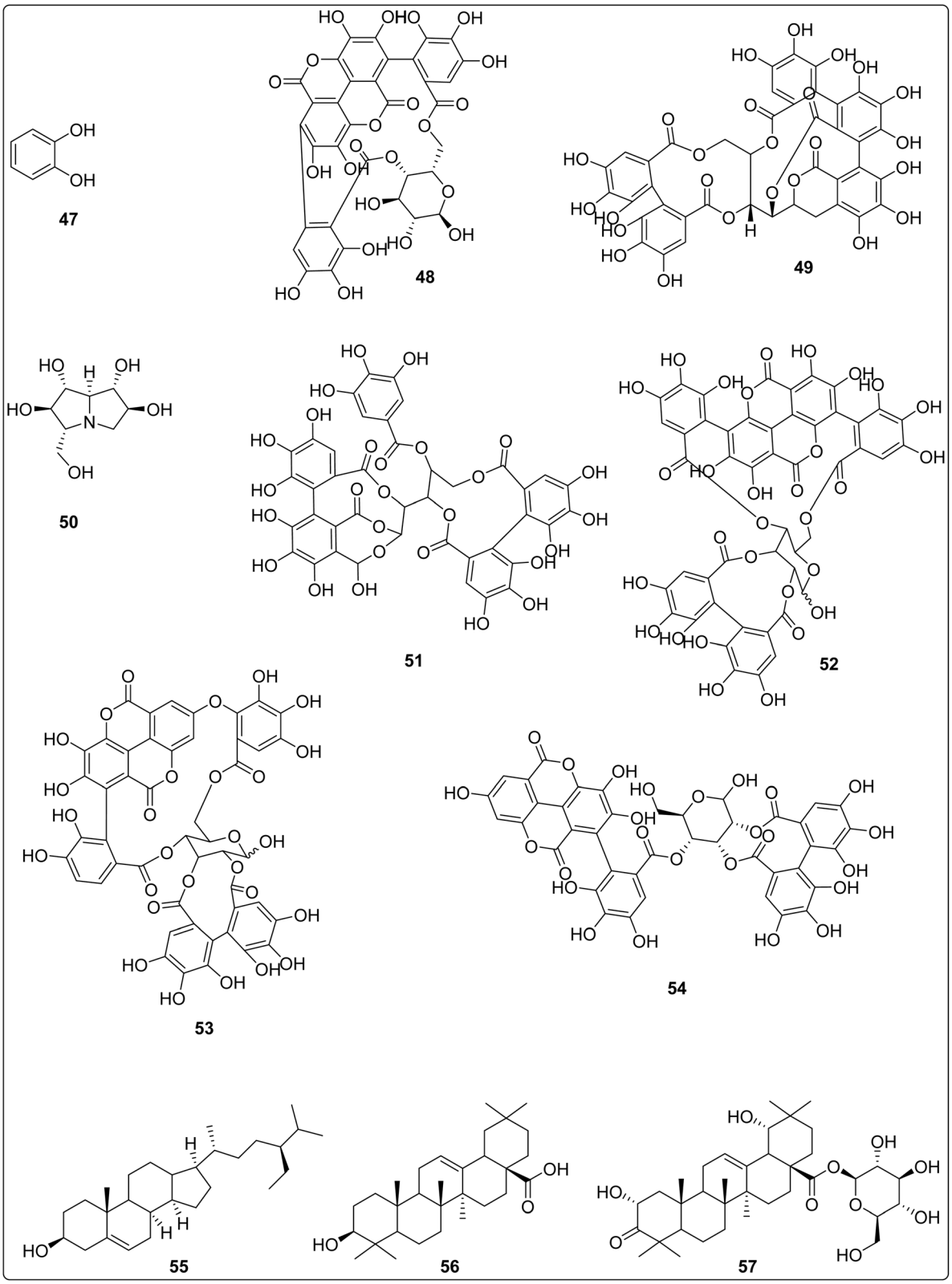

Fig. 2 (*Contd.*)

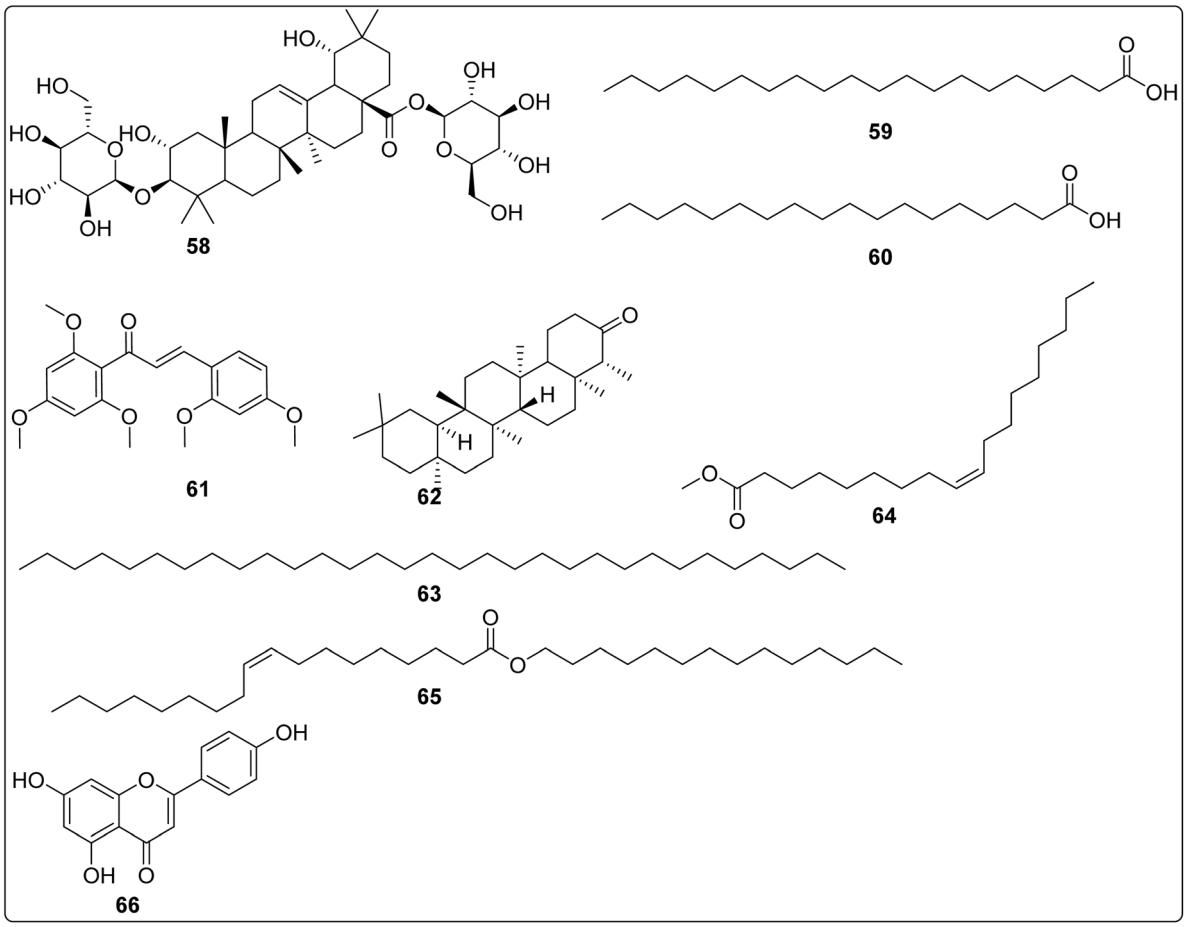

Fig. 2 (*Contd.*)

myocardial injury. The cardioprotective effects of *T. arjuna* were comparable to those of fluvastatin, a synthetic drug. The bark extract effectively attenuated cardiac dysfunction and myocardial damage by restoring endogenous antioxidant enzyme activity, reducing lipid peroxidation, and lowering cytokine levels.[94]

An alcoholic bark extract at a dose of 0.75 mg kg^{-1} body weight normalized *in vivo* myocardial injury in rats. In a double-blind, placebo-controlled study on chronic stable angina patients, *T. arjuna* bark extract improved treadmill and clinical exercise parameters compared to placebo, yielding results similar to isosorbide mononitrate therapy.[95] A 6 mg kg^{-1} dose of a 70% alcoholic extract of the bark produced a hypotensive effect in anesthetized dogs, which was blocked by propranolol, suggesting that active constituents in the extract may have adrenergic beta-2 receptor potential, directly affecting heart muscle and supporting its cardiovascular use in Ayurveda.[73]

Dilated cardiomyopathy with reduced left ventricular ejection fraction (LVEF), whether due to idiopathic or ischemic causes, showed significant improvement in left ventricular parameters and functional capacity with standard therapy supplemented by 50% ethanol extract of *T. arjuna* bark. In diabetic rats, 50% ethanol bark extract significantly mitigated cardiac dysfunction and myocardial injury, reducing oxidative stress, endothelin-1 (ET-1), and inflammatory cytokine levels. However, the decreased body weight, heart rate, blood pressure, and elevated blood sugar levels in diabetic rats did not improve with 50% ethanol bark extract therapy. These findings suggest that *T. arjuna* bark extract may enhance altered myocardial function in diabetic rats, possibly by maintaining endogenous antioxidant enzyme activities and reducing ET-1 and cytokine levels.[96]

1.3.2 Anti-cancer activity. Tannins, terpenoids and flavonoids from the leaves, bark, and stems of *T. arjuna* are reported as the primary contributors to its anti-cancer properties.[28] Acetone extract of bark containing tannins has been shown to inhibit mutagenicity in *Salmonella typhimurium*.[97] Methanolic and acetone extracts have been reported to inhibit the growth of transformed cells in normal human fibroblasts, osteosarcoma, and glioblastoma.[98] Additional studies suggest that ethyl acetate and acetone extracts, which contain both non-polar and polar compounds, display the highest mutagenic activity against the mutagen 4-nitroquinoline-N-oxide (4NQO) compared to chloroform and methanolic-HCl extracts, highlighting their anti-

cancer potential.[99] Comet assays and micronuclei tests indicate that acetone and methanolic extracts are more effective than others in reducing DNA damage caused by 4NQO.[99] Leaf extracts of *T. arjuna* also exhibit moderate cytotoxic activity against BT-20 human breast cancer cells.[27] Additionally, bark extracts were reported to protect DNA from ADR-induced damage, and aqueous stem bark extracts demonstrate antioxidant effects that reduce oxidative stress and inhibit anaerobic metabolism, contributing to anti-carcinogenic activity.[100] *In vitro* screening of petroleum ether bark extracts against two human cancer cell lines, HEP2 (liver) and HT29 (colon), using the Sulforhodamine B (SRB) assay showed growth inhibition rates of 78% and 79.33%, respectively.[101]

1.3.3 Anti-bacterial activity. Studies have shown that *T. arjuna* bark exhibits antibacterial properties. Methanolic leaf extracts of *T. arjuna* demonstrated strong antibacterial activity against multi-drug-resistant *Salmonella typhi*.[102] Research on the leaves and bark also indicated their potential to treat ear infections caused by bacteria.[103] Aqueous and methanolic extracts of *T. arjuna* effectively inhibited the growth of various bacterial species, including *E. coli*, *Klebsiella* sp., *Pseudomonas* sp., and *Staphylococcus* sp., in a dose-dependent manner.[104] Methanolic extracts from the fruit of *T. arjuna* also showed significant antibacterial activity against *Staphylococcus aureus* and *Pseudomonas aeruginosa*.[105] The *n*-butanol fraction of the methanolic extract of bark and the *n*-butanol fraction of the methanol extract of leaves exhibited strong antimicrobial effects against *Bacillus subtilis*, *E. coli*, *Klebsiella pneumonia*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Salmonella typhi*.[106]

Shreya *et al.* studied the bark extract of *T. arjuna* for its antimicrobial properties. Methanolic extracts of bark exhibited a stronger inhibitory effect against Gram-negative bacteria compared to Gram-positive bacteria.[107]

The ethanolic bark extract inhibited *Vibrio cholera* growth at all concentrations, with zone diameters increasing proportionally to concentration. Regression coefficients for the relationship between concentration and zone diameter ranged from 0.75 to 0.984 for most isolates, suggesting a linear relationship.[108]

Methanolic and water extracts of *T. arjuna* bark showed significant inhibition zones against 22 tested bacteria, including eight uropathogens, with minimum inhibitory concentration (MIC) values between 0.16 and 2.56 mg mL^{-1}. The chloroform extract showed no antibacterial activity. The aqueous extract of *T. arjuna* bark also demonstrated strong antifungal effects against eight Candida species, with MIC values ranging from 0.16 to 0.64 mg mL^{-1}. The high antimicrobial efficacy of polar extracts correlated with their elevated polyphenol content, in contrast to the non-polar chloroform fraction.[109]

Aqueous extracts of *Terminalia arjuna* (fruit, bark, root, and leaves) demonstrated notable antibacterial properties. The bark extract effectively inhibited the growth of both Gram-positive and Gram-negative bacteria. In contrast, the inhibitory effect of the leaf extract varied depending on the microorganism. Aqueous extracts from the leaves and fruits showed greater activity against Gram-negative bacteria compared to Gram-positive bacteria. Among the microorganisms tested, the highest inhibition was observed in *Escherichia coli*, followed by *Pseudomonas aeruginosa*, *Bacillus cereus*, *Bacillus subtilis*, and *Lactobacillus bulgaricus*. However, *Micrococcus glutamicus* and *Micrococcus luteus* exhibited lower sensitivity to the bark extract. Overall, the bark extract showed the strongest antibacterial activity across most strains, except for *M. glutamicus.* However, leaf and fruit extracts were not active toward any of the Gram-positive strains used in the study.[110]

Meena *et al.* evaluated the antimicrobial efficacy of sequentially fractionated solvent extracts from *T. arjuna* (Roxb) against key pathogens in aquaculture. The study examined solvent extracts from the bark, fruit, and leaves of *T. arjuna* against 17 bacterial isolates from various species and the fungus *Aphanomyces invadans*. The minimum inhibitory concentration (MIC) for the bacterial isolates ranged from 0 to 25 μg mL^{-1}, with an average of 11.39 ± 0.48 μg mL^{-1}. Among the extracts, the ethanolic bark extract demonstrated the largest inhibition zone (20.83 ± 0.10 mm), followed by the ethanolic fruit extract (19.50 ± 0.06 mm) against *Edwardsiella tarda*. The solvent extracts showed efficacy at concentrations of 0.5 mg mL^{-1} and 1 mg mL^{-1} for bacterial isolates and fungal strains, respectively. The chemical analysis identified prominent bioactive compounds, including ellagic acid (*m*/*z* 302.01), 18-glycyrrhetinic acid (*m*/*z* 470.34), azelaic acid (*m*/*z* 188.10), and caffeic acid (*m*/*z* 180.04), with a fit of over 80% in mzCloud analysis. Additionally, naringenin (*m*/*z* 272.06) was detected in the acetone bark extract, while kanamycin (*m*/*z* 426.35) and tetracycline (*m*/*z* 444.415) were present in the ethanol bark extract. Orientin (*m*/*z* 448.10) and phloretin (*m*/*z* 274.08) were identified in the leaf extracts. Results show that the ethanolic bark extract exhibited the most significant antimicrobial activity, followed by the methanolic bark extract.[111]

1.3.4 Antioxidant activity. The protective effects of ethanolic extracts of *T. arjuna* bark and its fractions (dichloromethane (TAD), ethyl acetate (TAE), butanol (TAB), and water (TAW)) were examined for their ability to counteract free radicals, protein oxidation, and DNA damage. The TAE fraction demonstrated the highest inhibition of DPPH, hydroxyl, ABTS, nitric oxide radicals, and metal chelation, with IC_{50} values of 270 ± 2 μg mL^{-1}, 175 ± 11 μg mL^{-1}, 25 ± 1.2 μg mL^{-1}, 82 ± 4 μg mL^{-1}, and 405 ± 9 μg mL^{-1}, respectively. According to the study, *T. arjuna* bark extracts ameliorated various impairments linked to DNA damage and free radical formation.[112]

The stem bark alcoholic extract of *T. arjuna* (ALTA) was also tested for antioxidant and antimutagenic (anticlastogenic) activities. ALTA displayed potent antioxidant properties with EC_{50} values of 2.491 ± 0.160 μM, 50.110 ± 0.150 μM, and 71.00 ± 0.250 μM in DPPH, lipid peroxidation, and superoxide radical scavenging assays, respectively, comparable to ascorbic acid (EC_{50} of 2.471 ± 0.140, 40.500 ± 0.390, and 63.00 ± 0.360). In a micronucleus test, ALTA (100 and 200 mg kg^{-1}, orally) significantly reduced the percentage of micronuclei in both normochromatic erythrocytes (NCE) and polychromatic erythrocytes (PCE) and showed a significant reduction in the P/N

ratio. These findings suggest that ALTA has notable antioxidant and antimutagenic effects.[113]

The free-radical scavenging capacity and antioxidant activity of bark extracts of *T. arjuna* (aqueous : ethanol (20 : 80 v/v) and aqueous : methanol (20 : 80 v/v)) were also evaluated, with extraction yields ranging from 6.66–19.09 g/100 g (w/w) on a dry-weight basis. The extracts contained substantial amounts of total phenolic content (TPC) at 6.02–11.00 g/100 g (as gallic acid equivalent) and total flavonoid content (TFC) at 1.75–5.96 g/100 g (as catechin equivalent). DPPH radical-scavenging activity had IC_{50} values of 2.71–7.68 μg mL^{-1}, inhibition of peroxidation ranged from 64.79 to 71.43%, and reducing power ranged from 0.001 to 1.584 mg mL^{-1}. These results indicate that *T. arjuna* bark extracts are a naturally rich source of antioxidants.[114] An *in vitro* model using goat red blood cells subjected to Cu^{2+}-ascorbate-induced oxidative stress demonstrated that aqueous *T. arjuna* bark extract reduced lipid peroxidation, increased the reduced glutathione levels, and decreased protein carbonyl content in treated RBCs. The aqueous extract also protected the activity of antioxidant enzymes catalase and superoxide dismutase (SOD) and exhibited scavenging effects on hydroxyl and superoxide anion radicals.[115] The effects of ethanolic extract (at doses of 250 and 500 mg kg^{-1} body weight) of *T. arjuna* stem bark were evaluated in alloxan-induced diabetic rats, specifically examining lipid peroxidation and enzymatic and non-enzymatic antioxidant activity in liver and kidney tissues. The extract significantly ($P < 0.05$) reduced lipid peroxidation (LPO), with the 500 mg kg^{-1} dose showing a greater effect than the 250 mg kg^{-1} dose. Additionally, the extract significantly ($P < 0.05$) increased levels of superoxide dismutase, catalase, glutathione peroxidase, glutathione-*S*-transferase, glutathione reductase, glucose-6-phosphate dehydrogenase, reduced glutathione, vitamins A, C, and E, as well as total sulfhydryl groups (TSH) and non-protein sulfhydryl groups (NPSH) in the liver and kidney of diabetic rats. These findings suggest that the extract exhibits antioxidant activity by mitigating oxidative stress, supporting the traditional use of this plant in managing diabetes.[116]

The aqueous extract of *T. arjuna* bark demonstrated protective effects on liver and kidney tissues against CCl_4-induced oxidative stress.[117] Methanol and ethanol extracts of *T. arjuna* seeds showed high antioxidant activity by inhibiting DPPH (88% ± 1.52% and 87% ± 0.057% inhibition, respectively), which was significant, although slightly lower than that of standard ascorbic acid (93.73% ± 1.12%).[118] Alcoholic extracts of the bark exhibited notable radical-scavenging activity against DPPH and nitric oxide radicals.[119]

In another study, oral administration of CCl_4 at a dose of 1 mL kg^{-1} body weight for 2 days significantly reduced the activities of antioxidant enzymes—catalase (CAT), glutathione-*S*-transferase (GST), and superoxide dismutase (SOD)—and depleted reduced glutathione (GSH) levels in cardiac tissue. Lipid peroxidation and oxidized glutathione (GSSG) levels were increased under these conditions. However, oral administration of the active constituents of *T. arjuna* (50 mg kg^{-1} body weight) for 7 days before CCl_4 exposure significantly restored antioxidant enzyme activities, increased GSH levels, and reduced lipid peroxidation products. The FRAP assay showed that the active constituents also enhanced intracellular antioxidant activity in cardiac tissue. Histological studies further supported the cardioprotective effects of these active constituents, which were comparable to those of vitamin C, a known antioxidant.[120]

Shreya *et al.* used thin-layer chromatography to separate the flavonoid components of *T. arjuna* and evaluated the phytochemical composition, antimicrobial activity, antioxidant activity, and total flavonoid content. Phytochemical screening was conducted using standard and commonly available tests. Antioxidant activity and the presence of flavonoid compounds were analyzed using thin-layer chromatography (TLC). Total antioxidant capacity was determined using the 2,2-diphenyl-1-picrylhydrazyl (DPPH) colorimetric assay. The methanolic extract showed significant antioxidant activity, as evidenced by a decrease in DPPH radical absorption during the scavenging assay. Flavonoid components with antioxidant properties were present in the methanolic extract at a concentration of 199.00 mg quercetin equivalent per gram of dried extract, as determined by the colorimetric method.[107]

Meena *et al.* investigated the antioxidant, free-radical scavenging, and DNA-nicking inhibition activities of 21 solvent extracts of *T. arjuna* under hydrogen peroxide (H_2O_2) conditions. The study revealed a strong positive correlation and interaction (explaining 84.54% variation in PCA 1) between 2,2-diphenyl-1-picrylhydrazyl (DPPH), ferric reducing antioxidant power (FRAP), 2,2′-azino-bis-3-ethylbenzothiazoline-6-sulphonic acid, and nitrous oxide scavenging (%) with ethanol bark extract (EBE) and methanol fruit extract (MFE). The total phenolic content (TPC) ranged from 144.67 to 1794 μg mL^{-1} (gallic acid equivalent, GAE), and total flavonoid content (TFC) ranged from 2.5 to 34 μM Fe(II)/g, with EBE exhibiting the highest values. Among the solvent extracts, EBE demonstrated the greatest antioxidant capacity, followed by ELE, MBE, and DWFE. The DNA nicking inhibition analysis showed significant positive correlations ($p < 0.01$) for relative front, relative quantity, band intensity (%), and lane intensity (%), with an R^2 value of 0.94. EBE was found to nick supercoiled, circular plasmid DNA effectively, showing comparable activity to standard antioxidants such as butylated hydroxyanisole, butylated hydroxytoluene, ascorbic acid, and gallic acid. Notably, gallic acid (m/z 170.0208) and ellagic acid (m/z 302.0063) were present in high concentrations in the extracts, with an effective concentration of 0.48 mg required for DNA nicking inhibition. This work also reports higher steroid concentrations in acetone, ethanol, and methanol bark fractions. It provides significant insights into the phytochemical composition, antioxidant potential, and DNA nicking inhibition properties of *T. arjuna* solvent extracts, which could aid in developing remedies for geriatric chronic diseases.[121]

1.3.5 Anti-inflammatory activity. The anti-inflammatory effect of *T. arjuna* was evaluated using the carrageenan-induced paw oedema method, revealing significant efficacy ($p < 0.001$) in acute inflammatory conditions at both 250 mg kg^{-1} and 500 mg kg^{-1} doses. The extract was also assessed for centrally acting analgesic effects through formalin and hot-plate tests and peripheral analgesic effects with the acetic acid-

induced writhing test in mice. At oral doses of 250 mg kg^{-1} and 500 mg kg^{-1}, 50% ethanolic bark extract of *T. arjuna* demonstrated significant analgesic activity ($p < 0.01$; $p < 0.001$) across these models. In the hot-plate test, both dose levels showed a significant increase in latency period ($p < 0.001$) compared to the control group. Additionally, in the acetic acid-induced writhing and formalin tests, *T. arjuna* significantly reduced the number of writhes at both dose levels ($p < 0.05$; $p < 0.001$) relative to the control.[122]

In vitro studies suggested that methanol extracts of *T. arjuna* leaves and fruits had a stronger anti-inflammatory effect than the methanol extract of the bark, potentially due to high levels of saponins, tannins, and flavonoids, which may contribute to HRBC membrane stabilization and anti-inflammatory activity.[123] Oral administration of *T. arjuna* fruit aqueous extract demonstrated an acute anti-inflammatory effect in carrageenan-induced paw oedema, along with analgesic effects in acetic acid-induced writhing and heat-induced pain tests, indicating both central and peripheral mechanisms by inhibiting the biosynthesis and/or release of pain mediators.[124]

Studies found that bark powder of *T. arjuna* in formulations such as Arjuna Ksheera Paka (AKP) and hydroalcoholic (HA) extracts exhibited significant anti-inflammatory activity ($p < 0.05$) in reducing paw oedema in mice. HA was more effective in the early phase of inflammation, while AKP demonstrated greater efficacy in the late phase, potentially due to the presence of milk solids in AKP.[125]

Pre-treatment with methanolic extracts of *T. arjuna* leaves (200 and 400 mg kg^{-1}) reduced paw oedema by 38.05% and 64.95%, respectively, and decreased granulomatous tissue weight to 115.33 mg and 73.67 mg. Haematological analysis of pre-treated animals showed decreased white blood cells (WBC) and platelet counts with increased Hb and RBC levels. Methanolic leaf extract pre-treatment also reduced nitrite and lipid peroxidation (LPO) levels while increasing antioxidant enzymes, such as superoxide dismutase (SOD), glutathione synthetase (GSH), and glutathione peroxidase (GPx). Histopathology revealed a decrease in inflammatory cell accumulation with methanolic leaf extract treatment.[126] Additionally, *T. arjuna* bark powder (400 mg kg^{-1}, orally) significantly minimized formalin-induced paw oedema at 24 hours.[127]

1.3.6 Anti-diabetic activity. *T. arjuna* has been explored for its anti-diabetic roles since ancient times.[128] The aqueous stem bark extract of *T. arjuna* demonstrated anti-diabetic activity by increasing granulocyte count and reducing free haemoglobin and total cellular content in diabetic human blood and plasma samples.[129] In an *in vivo* study, the acetone extract of *T. arjuna* bark showed protective effects on blood glucose levels, oral glucose tolerance (OGTT), and insulin tolerance in streptozotocin (STZ)-treated rats. Rats fed with 500 mg kg^{-1} body weight of the bark extract exhibited significantly ($P < 0.05$) improved parameters compared to diabetic control rats and those fed with 250 mg kg^{-1}, with no significant difference compared to glimepiride-treated rats. The 500 mg kg^{-1} dosage showed greater anti-hyperglycemic and anti-diabetic effects ($P < 0.05$) than the 250 mg kg^{-1} dosage.[130] Treatment with the acetone extract of the root of *T. arjuna* significantly reduced elevated levels of total cholesterol (TC) and triglycerides (TG) compared to negative controls in diabetic animals. This study indicated that both extract and glibenclamide protected diabetic rats from substantial body weight loss when administered orally for 15 days.[131]

Further evaluation of *T. arjuna*'s anti-diabetic effects showed that its root extract has potent antidiabetic effects in alloxan-induced diabetic rats. A 50% ethanol extract of the stem bark, administered at 1.25 g kg^{-1} body weight for 21 days to type 2 diabetic Long-Evans rats, significantly ($p < 0.05$) improved glucose tolerance by the end of this study compared to controls. Fasting serum glucose levels also decreased significantly ($p < 0.05$) after 21 days of treatment, though no changes were observed in liver glycogen content or serum insulin levels. Additionally, *T. arjuna* stem bark 50% ethanolic extract showed beneficial effects on lipid profiles, significantly reducing serum total cholesterol and triglyceride levels ($p < 0.01$ and $p < 0.001$, respectively). Glibenclamide (5 mg kg^{-1}) similarly produced a significant reduction ($p < 0.01$) in serum glucose in type 2 diabetic rats.[132]

The hydroethanolic extract of *T. arjuna* bark exhibited α-amylase inhibitory activity, with an IC_{50} of 145.90 μg mL^{-1} compared to the IC_{50} of acarbose 62.35 μg mL^{-1}, suggesting that α-amylase inhibition might contribute to its antidiabetic effect through the synergistic action of its phytochemicals.[133]

T. arjuna also showed efficacy in managing diabetes with cardiovascular complications, helping to restore body weight in treated rats compared to controls. The hydroalcoholic extract of *T. arjuna* bark (HATAB) treatment significantly reduced hyperglycaemia compared to the diabetic ISP control (D-ISP) group, though Vildagliptin (VIL) showed a superior effect. Rats treated with both VIL and (HATAB) had a significantly lower heart-to-body weight ratio compared to the D-ISP group. Combined VIL and HATAB extract treatment reversed STZ/ISP-induced increases in CPK-MB and hs-CRP levels. Serum CPK-MB isoenzyme and hs-CRP levels were significantly lower in treated rats, indicating reduced cardiac damage. Moreover, VIL and treatment with HATAB extract significantly reduced serum DPP-4 levels in D-ISP rats, with a positive correlation between cardiac marker CPK-MB and serum DPP-4 confirmed by histopathology (VIL, $r = 0.899$; $p < 0.01$; bark, $r = 0.848$; $p < 0.05$).[134]

T. arjuna bark aqueous extract also stimulated insulin release alone ($p < 0.001$) and in combination with other modulators, though this effect required extracellular Ca^{2+}. The extract increased intracellular calcium without affecting depolarized cells and significantly enhanced glucose uptake ($P < 0.001$). At higher concentrations, it inhibited both starch digestion and protein glycation ($p < 0.001$).[135]

1.3.7 Hepatoprotective activity. *T. arjuna* has been reported to exhibit hepatoprotective activity against paracetamol-induced hepatic injuries.[136–139] Administration of aqueous extracts of *T. arjuna* bark before paracetamol/CCl_4 administration led to a significant reduction in sGOT, sGPT, sALP, and SB levels, almost comparable to silymarin in CCl_4-induced hepatocarcinoma. Histopathological examination of liver tissue from control and treated animals further confirmed the hepatoprotective effect.[140] Another study indicated that methanolic

extracts of *T. arjuna* stems and their phytochemicals also exhibit hepatoprotective activity. CCl_4 treatment caused a marked increase in serum glutamate pyruvate transaminase (GPT) and alkaline phosphatase (ALP) levels, as well as in thiobarbituric acid reactive substances (TBARS) levels, while reducing catalase (CAT), glutathione-*S*-transferase (GST) and superoxide dismutase (SOD) levels in liver and kidney tissue homogenates of treated mice. The aqueous extract of *T. arjuna* bark successfully prevented these adverse changes in experimental animals.[141]

1.3.8 Insect repellent activity. The repellent and antifeedant effects of *Saraca asoca* and *T. arjuna* bark extracts were evaluated for controlling *Sitophilus oryzae*. The methanol extract of *T. arjuna* bark exhibited a stronger repellent effect against *S. oryzae* adults compared to the *Saraca asoca* bark extract. Additionally, the methanol extract of *T. arjuna* bark demonstrated greater antifeedant activity against *S. oryzae* adults than the *Saraca asoca* bark extract. These insecticidal, repellent, and antifeedant properties in *Saraca asoca* and *T. arjuna* bark extracts may be attributed to their bioactive compounds.[142]

1.3.9 Wound-healing activity. The wound-healing properties of two herbal formulations (Himax ointment and lotion) containing *Indradaru* extract, specifically *T. arjuna* bark (Family: Combretaceae), were evaluated in two wound models in rats: (i) excision and (ii) incision. Both formulations showed significant activity in both wound models. Their effects were comparable to those of the standard drug nitrofurazone, particularly in terms of wound contraction, epithelialization period, tensile strength, and tissue regeneration at the wound site.[143]

Meenakshi *et al.* prepared a 50% aqueous alcohol extract of *T. arjuna* bark and fractionated this extract to obtain a tannin-rich fraction. The effects of topical application of this tannin-rich fraction were also assessed on rat dermal wounds *in vivo*. The findings showed a statistically significant increase in tensile strength in incision wounds and in epithelialization percentage in excision wounds compared to the control ($p < 0.05$).[144]

Additionally, wound-healing effects of a 50% ethanolic extract of *T. arjuna* bark and tannins isolated from the bark were investigated in incision and excision models following oral or topical application as a hydrogel. The results showed a statistically significant increase in tensile strength in incision wounds and a greater reduction in wound size in excision wounds compared to the control. Topical treatment with tannins was particularly effective in both models, with an increase in hydroxyproline content in the granulation tissue of excision wounds, indicating enhanced collagen turnover and accelerated wound healing.[145]

1.3.10 Food and nutrition. Meena *et al.* assessed the nutritional value of *T. arjuna* through a 90-days experiment designed to optimize the use of *T. arjuna* bark powder (TABP) in the diet of *Labeo rohita*. Four iso-nitrogenous diets (305.74 g crude protein per kg diet) and iso-caloric diets (18.15 MJ gross energy per kg diet) were formulated, incorporating TABP at levels of 0.0, 5.0, 10.0, and 15.0 g kg^{-1} feed, designated as TABP0, TABP5, TABP10, and TABP15, respectively. A total of 540 juvenile fish (average weight 20.7 g, 45 fish per tank) were randomly distributed into 12 fiber-reinforced plastic (FRP) tanks, each with a 500-Liter water capacity. Fish were fed to satiation twice daily, at 9:30 AM and 5:00 PM. The results indicated that diets containing 10 g TABP per kg feed produced the highest growth rates (weight gain percentage and specific growth rate), nutrient utilization (protein efficiency ratio, apparent net protein utilization, fat retention, and energy retention), and survival rate. In contrast, the feed conversion ratio (FCR) displayed an inverse relationship ($P < 0.05$) with growth rates. Growth rates, feed conversion, and nutrient utilization were comparable between the TABP0 and TABP15 groups ($P > 0.05$). The viscerosomatic index (VSI) and craniosomatic index (CSI) were significantly affected ($P < 0.05$), while the hepatosomatic index (HSI) showed no significant changes ($P > 0.05$). Whole-body composition was significantly influenced ($P < 0.05$), except for ash content ($P > 0.05$). Furthermore, the RNA content and the RNA : DNA ratio were positively correlated with growth rates and nutrient retention ($P < 0.05$). The study concluded that TABP, at an optimal inclusion level of 12.3 g kg^{-1} feed, can effectively produce healthy, high-quality fish for human consumption, termed "Green Fish." This research also provides a foundation for developing TABP-based medicated feeds on a larger scale, which could be tested under field conditions alone or in combination with commercial feeds.[146]

Meena *et al.* also assessed the impact of processing and pretreatment on the biochemical composition, mineral profiling, and yield (%) of selected solvent extracts of *T. arjuna* (Arjuna). The analysis revealed that the maximum yield was obtained from the ethanolic bark extract in both individual (23.6% ± 0.026%) and serial (22.23% ± 0.017%) fractions. The yield of ethanolic and methanolic bark extracts showed no significant difference ($p \geq 0.05$), whereas non-polar solvent extracts exhibited significant differences ($p \leq 0.05$). Mineral profiling demonstrated substantial variation between dry powders and their solvent extracts. Fractionation increased the zinc (Zn) content in fruit extracts, with the methanolic extract recording the highest Zn level (45.29 mg L^{-1}). An inverse relationship between ash and moisture content was observed across all solvent extracts. The maximum ash content was recorded in the bark powder, with values of 28.95% ± 0.001% (serial fraction) and 28.19% ± 0.008% (individual fraction). However, ash content did not directly correlate with mineral profiling, suggesting higher acid-insoluble ash levels in bark compared to leaves and fruit. This may contribute to the bio-efficacy of the solvent extracts.

The findings indicated that the inherent medicinal properties of *T. arjuna* bark can be leveraged, and its solvent extracts could be utilized in drug formulation. The study highlights the potential to enhance mineral profiling, particularly zinc—a potent neurotransmitter—which could be used to develop suitable feeds for livestock and fisheries. Furthermore, these findings provide a pathway for addressing nervous disorders in human health through dietary supplementation or therapeutic formulations.[147]

Pankaj *et al.* developed a process utilizing *T. arjuna* bark extract to produce herbal ghee from buffalo milk. Three types of extracts were evaluated: commercially available aqueous *arjuna* extract powder, laboratory-prepared aqueous extract, and

alcoholic extract. Among these, ghee produced with the alcoholic extract (at a 4% fat-to-extract ratio) was found to be superior in quality. To optimize the level of the alcoholic extract to maximize phytosterol retention in ghee, samples were prepared using extract concentrations of 5%, 6%, and 7% relative to the weight of fat. No significant difference in sensory acceptability scores was observed among these levels. However, phytosterol content was highest (0.38 mg g^{-1} with cream as the fat source and 0.47 mg g^{-1} with butter) at the 7% extract level. The optimized herbal ghee was prepared using 7% alcoholic *arjuna* extract with the creamery butter method. Its chemical composition included 99.92% fat, 0.08% moisture, 0.22% free fatty acid (as oleic acid), a butyro-refractometer reading of 41.5 at 40 °C, a Reichert-Meissl value of 31.5, and a phytosterol content of 0.39 mg g^{-1}. This process demonstrates the potential of incorporating *arjuna* extract into ghee for enhanced phytosterol content and associated health benefits.[148]

Suman *et al.* developed buffalo meat rolls by incorporating extracts from *T. arjuna* bark and *Aloe vera* gel at varying levels (2%, 4%, and 6%) to determine the optimal incorporation rate and evaluate their effects on the texture profile of the products. Meat rolls containing 4% *Aloe vera* gel scored slightly higher in juiciness and tenderness compared to those with 2% *T. arjuna* bark extract. However, no significant differences were observed between these two samples in overall sensory scores, which were comparable to the control. Based on sensory evaluations, 4% *Aloe vera* gel and 2% *T. arjuna* bark extract were identified as the optimal levels for incorporation and were selected for further study. The texture attributes of the developed products, such as hardness, springiness, and cohesiveness, were comparable with those of the control samples. The study concluded that buffalo meat rolls with desirable sensory and textural properties can be successfully developed by incorporating 4% *Aloe vera* gel and 2% *T. arjuna* bark extract, enhancing the product's overall quality.[149]

Pravin *et al.* evaluated the hypolipidemic and antioxidant properties of a vanilla-chocolate dairy drink fortified with encapsulated *T. arjuna* bark powder (1.8%) in Wistar rats fed a high-cholesterol diet for 60 days. By the conclusion of the experimental period, a significant lowering in body weight gain was observed in rats administered with the encapsulated herb extract when compared to those on a high-cholesterol diet without supplementation. Additionally, microencapsulation of the herb resulted in a significant reduction in organ weights, particularly epididymal fat and liver. The supplemented group exhibited notable reductions in serum lipid levels, including total cholesterol, triglycerides, low-density lipoprotein (LDL), very-low-density lipoprotein (VLDL), and the atherogenic index. Encapsulation also enhanced antioxidant activity, evidenced by increased reduced glutathione levels and decreased thiobarbituric acid reactive substances (TBARS) in liver tissues and red blood cell lysates. The findings highlighted that the bioactive compounds in encapsulated *T. arjuna*—such as phytosterols, flavonoids, saponins, and tannins—remained stable during processing and were effectively released in the intestine. These compounds contributed to its hypolipidemic and antioxidant effects, offering therapeutic potential for managing cardiovascular diseases.[150]

Various groups have also formulated herbal tea with the extracts of *T. arjuna*, along with other herbal extracts. These products are commercially available and known to have several health benefits.[151,152]

1.3.11 Immunomodulatory effects. Meena *et al.* explored the dietary immunomodulatory effects of *T. arjuna* bark powder (TABP) in *Labeo rohita*, a freshwater fish model. Fish were fed four iso-nitrogenous and iso-caloric diets containing graded levels of TABP (0, 5, 10, and 15 g kg^{-1}) for 90 days, followed by a 10-days challenge with the pathogenic bacteria *Aeromonas hydrophila* and *Edwardsiella tarda*. The study employed an Integrated Biomarker Response (IBR) approach to evaluate hematological, adaptive, and humoral immune parameters alongside liver histomorphology. Dietary inclusion of TABP at 10 g kg^{-1} significantly improved ($p < 0.05$) hematological indices (hemoglobin levels, red blood cell count, and hematocrit), specific immune responses (lysosomal enzyme activity, phagocytosis, and respiratory burst), and non-specific immune parameters (serum lysozyme and alternative complement activity). Additionally, liver histomorphology showed structural improvements indicative of enhanced immune function. A broken-line regression analysis identified 11.5 g kg^{-1} as the optimal dose, while 15 g kg^{-1} resulted in a slight decline in some parameters, suggesting a dosage threshold for TABP's efficacy. These findings highlight TABP's potential as a natural immunomodulator in fish aquaculture.[153]

In a related study by the same group, a nutritional fish feed incorporating TABP was administered to *Labeo rohita* at varying levels: 0% (0 g kg^{-1}, CT), 0.5% (5 g kg^{-1}, T1), 1% (10 g kg^{-1}, T2), and 1.5% (15 g kg^{-1}, T3). A comprehensive biomarker response strategy was used to assess the genomic impact of TABP inclusion. Following bacterial infection, the expression of immunogenic genes—STAT1 (signal transducer and activator of transcription 1), ISG15 (interferon-stimulated gene 15), and Mx (myxovirus resistance gene)—was elevated. Densitometry analysis revealed a dose-dependent increase in STAT1 and ISG15, with Mx reaching its highest levels at 10 g kg^{-1} TABP.[154]

1.3.12 Toxicology. Khurram *et al.* examined the toxicity profile of arjunolic acid (AA) in healthy female Sprague Dawley rats. In this study, AA was administered orally in single doses of 300 mg kg^{-1} and 2000 mg kg^{-1} body weight to groups 1 and 2, respectively, while group 3 served as the control. The animals were monitored for two weeks for any behavioural or physical changes. On the 15th day, blood samples were collected for hematological and biochemical analysis, and the animals were euthanized to harvest organs for histopathological examination. Histological alterations in tissues were assessed using four staining methods: hematoxylin and eosin, Masson trichrome, periodic acid-Schiff (PAS), and Oil Red O. The study observed no morbidity or mortality in the treated groups at either dose level. Daily food and water intake, body weight, relative organ weight, hematological, and biochemical parameters remained within normal ranges. Histopathological analysis revealed no significant structural changes in tissues. These findings highlight the

safety profile of AA, demonstrating that it is well tolerated even at high doses.[155]

Meena *et al.* conducted an *in vitro* toxicity study to validate, standardize, and supplement data on the toxicity assessment of various solvent extracts of *T. arjuna* using *Artemia salina* as a model organism. Experimental conditions were optimized, including the use of 100 W yellow light, 5% salinity, pH 8.0–8.5, and a temperature of 30 °C, over 48 hours. Nauplii were collected using a modified dropper and incubated for 24 hours under the same conditions before being observed with a 50× magnifying glass. Functional screening of solvent extracts and their respective mother solvents revealed LC_{50} values for hexane (118.50 ppm), ethyl acetate (101.75 ppm), chloroform (93.36 ppm), acetone (278.32 ppm), ethanol (528.78 ppm), and methanol (477.67 ppm). These values categorized the solvents as medium, medium, high, medium, low, and medium toxicity, respectively. Interestingly, the toxicity of the solvent extracts differed from their mother solvents, demonstrating the extracts' effectiveness. Universal solvents, such as DMSO and distilled water (DW), were classified as non-toxic according to Meyers' toxicity index and Clarkson's toxicity criterion. Among the solvent extracts of *T. arjuna*, all were toxic per Meyers' toxicity index but varied in toxicity classification under Clarkson's criterion, ranging from low to high toxicity. Principal Component Analysis (PCA) revealed strong correlations, with PCA1 and PCA2 explaining 69.46% and 19.74% of the variation, respectively. The study concluded that LC_{50} values could be categorized as relative LC_{50} (linked to the mother solvent) or absolute LC_{50} (actual extract potential). Relationships between relative and absolute LC_{50} values were linear, with their percentage fractions and inversely related to their counterparts.[156]

1.3.13 Generation of nanoparticles using leaves and bark of *T. arjuna* and their biological properties. Several studies have explored the green synthesis and applications of nanoparticles using *T. arjuna* bark and leaf extracts.

Anuradha and colleagues reported the biosynthesis of copper (CuNPs) and zinc (ZnNPs) nanoparticles using aqueous *T. arjuna* bark extract as a reducing and stabilizing agent. The nanoparticles, characterized using UV-visible spectroscopy, FTIR, and SEM, were found to be spherical, with CuNPs ranging from 10 to 26 nm and ZnNPs from 15 to 25 nm. XRD analysis confirmed their structure. The antibacterial activity of the CuNPs was observed to be superior to that of ZnNPs against the tested organisms, although *Klebsiella pneumoniae* showed higher resistance. Both nanoparticles demonstrated antihaemolytic activity, with CuNPs being more effective.[157]

Amol and collaborators described the synthesis of gold nanoparticles (AuNPs) using *T. arjuna* leaf extract, with UV-visible spectroscopy showing a characteristic peak at 530 nm. TEM analysis revealed AuNPs with sizes of between 15 and 30 nm. The synthesized nanoparticles exhibited antibacterial activity against *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Salmonella typhimurium*.[158]

Rakhi *et al.* demonstrated the synthesis of AuNPs using bark extract under mild conditions at room temperature. Characterization through HRTEM, AFM, and XRD confirmed their structural properties. These nanoparticles were successfully used to catalyze the reduction of 4-nitrophenol to 4-aminophenol.[159]

Gopinath and his team synthesized spherical AuNPs (20–50 nm) using leaf extract and reported their characterization by UV-visible spectroscopy, FTIR, and TEM. These nanoparticles promoted mitotic cell division and pollen germination without cytotoxic effects.[160]

Natarajan *et al.* utilized ethanolic bark extract to synthesize AuNPs (20–50 nm), which were found to possess neuroprotective properties. Characterization techniques, including UV-visible spectroscopy and TEM, confirmed their stability and size. The nanoparticles demonstrated antioxidant, anticholinesterase, and anti-amyloidogenic activities, highlighting their potential for treating neurodegenerative disorders such as Alzheimer's disease.[161]

Akther and colleagues developed silver nanoparticles (AgNPs) through microwave-assisted green synthesis using bark extract. These nanoparticles showed significant antibacterial and anti-biofilm activity against multidrug-resistant *Escherichia coli*, including strains harbouring the CTXM-15 gene. Docking studies revealed strong interactions of phytochemicals with CTXM-15, inhibiting its expression.[162]

Koparde *et al.* synthesized AgNPs (40–50 nm) using bark extract and confirmed their formation through colorimetric and SEM analyses. These nanoparticles exhibited strong antibacterial activity, especially against *Pseudomonas aeruginosa*.[163]

Yallappa *et al.* employed a microwave-assisted method to produce AgNPs (10–15 nm) using bark extract. The synthesized nanoparticles demonstrated excellent antioxidant and antibacterial properties against bacteria and yeast.[164]

Sakheel and colleagues reported a simple "one-pot" synthesis of AgNPs using leaf extract, without additional stabilizers. FTIR analysis confirmed bio-capping by plant biomolecules. The nanoparticles exhibited antibacterial efficacy, making them suitable for biomedical applications such as wound treatment.[165]

Chabbi and collaborators synthesized palladium nanoparticles (PdNPs) using *T. arjuna* bark extract. Characterized by UV-visible spectroscopy and TEM, these PdNPs demonstrated catalytic efficiency in C–C coupling reactions and dye degradation.[166]

These findings collectively highlight the ability of *T. arjuna* extracts to facilitate the environmentally friendly synthesis of nanoparticles with significant applications in medicine, catalysis, and environmental remediation.

1.3.14 *T. arjuna* extracts in drug delivery. Gaikwad *et al.* investigated the potential of *T. arjuna* bark for transdermal drug delivery applications. Transdermal patches loaded with *T. arjuna* bark extract were developed using the solvent casting technique, incorporating varying amounts of chitosan and Eudragit RL 100, according to a 3^2 factorial design. These patches were evaluated for physicochemical properties, drug content, *in vitro* and *ex vivo* diffusion, skin irritation, and stability. Infrared spectroscopy confirmed that no chemical interactions or compositional changes occurred during patch preparation. The optimized batch (S3) exhibited drug release rates of 74.56% *in vitro* and 69.12% *ex vivo* over 12 hours. Skin irritation studies demonstrated that neither

the extract nor the excipients caused adverse effects. Stability testing revealed that the transdermal matrix formulations remained stable during storage. The study concluded that these formulations, containing different polymeric components, are suitable for transdermal delivery in treating chronic conditions such as cardiovascular disorders.[167]

Sobia *et al.* developed and characterized a pH-triggered *in situ* gelling system using moxifloxacin HCl (MOX-HCl). The gelling system utilized gum extracted from *T. arjuna* bark resin, blended with sodium alginate as the gelling agent. Sterilized formulations were prepared and assessed for their physicochemical properties, microbiological activity, and eye irritation potential. The drug-loaded *in situ* gel appeared as a clear solution, which transformed into a gel in the presence of tear fluid. The optimized formulation was stable, therapeutically effective, non-irritating, and exhibited sustained drug release for up to 12 hours. In rabbit studies, the gel caused no irritation symptoms such as redness, inflammation, or excessive tearing compared

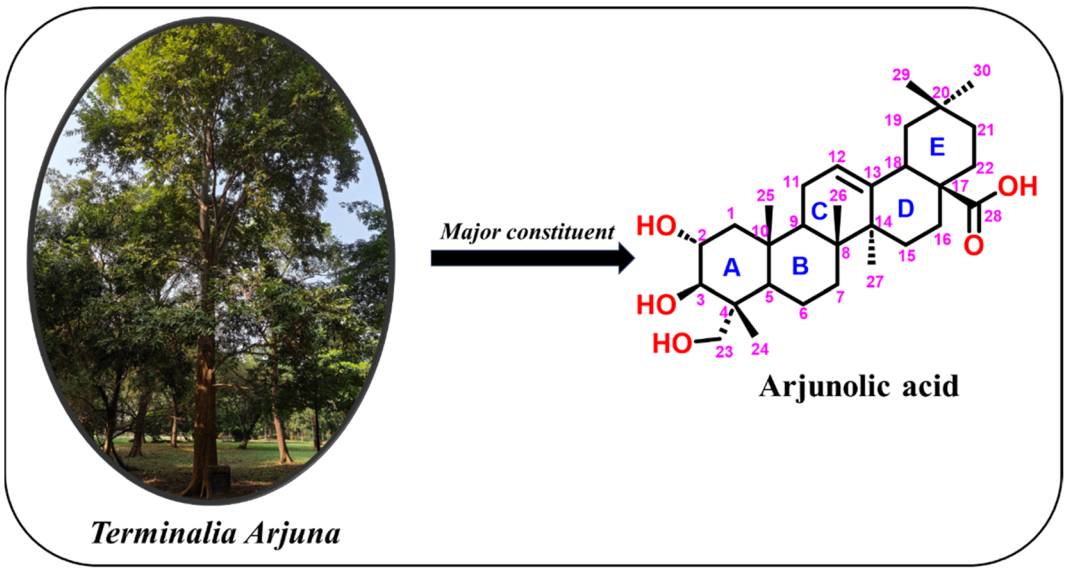

Fig. 3 Arjunolic acid, a pentacyclic triterpene acid, is a major constituent of *Terminalia arjuna*.

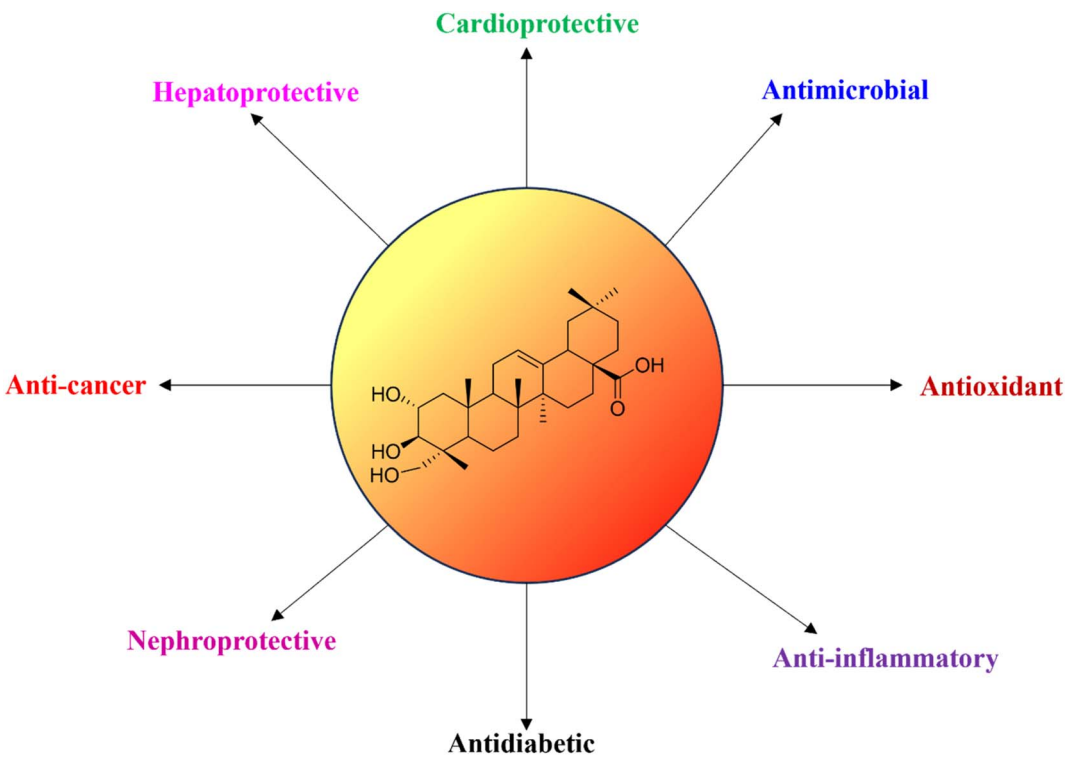

Fig. 4 Medicinal properties exhibited by arjunolic acid.

Table 2 Sources and methods of isolation of arjunolic acid with the corresponding yields

S. No	Source	Part	Method	Qty. of raw material used	Isolated quantity (% yield)	Ref.
1	*T. arjuna*	Heartwood	Column chromatography	—	—	169
2	*T. arjuna*	Stem bark	Column chromatography	1.5 kg	400 mg (0.04%)	170
3	*T. arjuna*	Stem bark	Column chromatography	2 kg	210 mg (0.01%)	171
4	*T. arjuna*[a]	Heartwood	Flash column chromatography	1 kg	15 g	172
5	*T. arjuna*	Bark	HPTLC	—	—	173
6	*T. arjuna*	Bark	HPLC-PDA	—	—	174
7	*T. arjuna*	Stem bark	Column chromatography	1 kg	250 mg (0.025%)	175
8	*T. arjuna*	Heartwood	Flash column chromatography	1 kg	11.5 g (1.15%)	7 and 176
9	*Akebiae fructus*	—	UHPLC-QTOF-MS	—	—	177
10	*Tilia kiusiana*	Leaves	Column chromatography	187 g	3.5 mg (0.002%)	178
11	*T. catappa*	Stem bark	MPLC	—	—	179
12	*Combretum griffithii*	Stem bark	Column chromatography	4.1 kg	127 mg (0.003%)	180
13	*Lagerstroemia indica*	Stem	Column chromatography	5 kg	2 mg (0.00004%)	181
14	*Shuang-Huang*-Lian	—	UHPLC -QTOF	—	—	182
15	*Wuzi-Yanzong-Wan*	—	UPLC-ESI-LTQ-orbitrap-MS	—	—	183
16	*Combretum racemosum*	Air dried pericarp	Column chromatography	9 kg	184 mg (0.002%)	184
17	*Premna odorata*	Leaves	LC–HRESIMS	—	—	185
18	*Folium eriobotryae*	—	—	—	—	186
19	*Bixa orellana* L	Root	Extraction/Separation	—	—	187
20	*Quercus serrata* Thunb[a]	Seeds/acorn	Column chromatography	30 kg	8.6 mg (0.0003%)	188
21	*Quince (Cydonia vulgaris)*	Peels	Column chromatography	3.1 kg	7.9 mg (0.002%)	189
22	*Phlomis umbrosa*	Root	Column chromatography	15 kg	9.4 mg (0.006%)	190
23	*Juglans sinensis*	Leaves and twigs	Column chromatography	20 kg	500 mg (0.002%)	191
24	*Cleistocalyx operculatus*[a]	Leaves	Column chromatography	3.3 kg	60 mg (0.002%)	192
25	*Stauntonia hexaphylla*	Fruit	Column chromatography	—	—	193
26	*T. albida*	Root	Column chromatography	470.9 g	7.4 mg (0.002%)	194
27	*Poraqueiba sericea*	Stems	Column chromatography	856 mg	2 mg (0.23%)	195
28	*Combretum nelsonii*[a]	Leaves	Column chromatography	12.38 g	81 mg (0.65%)	196
29	*Myrica adenophora*	Root	MPLC	7.2 kg	110 mg (0.002%)	197
30	*Myrcia rubella* Cambess	Leaves	Extraction/HPLC	320 g	0.3 mg (0.0009%)	198
31	*T. bentzoe* L	Leaves	Flash column chromatography	1.5 kg	20 mg (0.0013%)	199
32	*Clidemia hirta*	Root	HPLC	—	—	200
33	*Psidium guajava* L[a]	Leaves	Column chromatography	—	—	201
34	*Mosla dianthera*	Whole herb	Column chromatography	4.4 kg	80 mg (0.0018%)	202
35	*Eugenia jambolana* Lam	Berry/fruit pulp	Prep HPLC/column chromatography	500 g	8.2 mg (0.0016%)	203
36	*Glochidion assamicum*	Aerial parts	Column chromatography	14 kg	3 mg (0.00002%)	204
37	*Melandrium firmum*	Areial parts	Column chromatography	10 kg	13.5 mg (0.00013%)	205
38	*Duabanga grandiflora* L	Stem	Column chromatography	5 kg	162 mg (0.003%)	206
39	*Gentiana scarba*	Root and rhizomes	Column chromatography	2.5 kg	45.9 mg (0.0018%)	207
40	*Cyclocarya paliurus*	Leaves	HPLC-QTOF-MS	—	—	208
41	*Lagerstroemia. guilinensis*	Branches	Column chromatography	—	—	209
42	*Melaleuca alternifolia*	Bark and stem	Column chromatography	700 g	3.9 mg (0.0005%)	210
43	*Combretum leprosum*	Root	Column chromatography	—	—	211
44	*Vaccinium emarginatum*	Whole plant	Column chromatography	17.4 kg	36.4 mg (0.0002%)	212
45	*Juglans mandshurica*[a]	Green walnut husk	Column chromatography	10 kg	5.2 mg (0.0005%)	213
46	*Akebia trifoliata*	Areial parts	Column chromatography	—	—	214
47	*Siphoneugena densiflora*	Stem	Column chromatography	60.1 g	12 mg (0.019%)	215
48	*Eucalyptus globulus*[a]	Stem bark	GC-MS	—	—	216
49	*Osmanthus fragrans*[a]	Fruits	UHPLC-TQUAD-MS	—	—	217
50	*Miconia trailii*	Twig/leaves	Column chromatography	370 g	5 mg (0.0013%)	218
51	*Psidium guajava*[a]	Leaves	Column chromatography	20 kg	3 mg (0.00001%)	219
52	*Combretum nelsonii*[a]	Leaves	Column chromatography	500 g	81 mg (0.016%)	220
53	*Rubus sanctus and Rubus ibericus*	Leaves	UHPLC-ESI/HRMS	—	—	221
54	*Sapium haematospermum*	Aerial parts	HPLC	850 g	3 mg (0.0003%)	222
55	*Carissa opaca*	Whole plant	Column chromatography	10 kg	17 mg (0.00017%)	223
56	*Cola rostara* K. Schum	Root	Column chromatography	2.5 kg	10 mg (0.004%)	224

Table 2 (*Contd.*)

S. No	Source	Part	Method	Qty. of raw material used	Isolated quantity (% yield)	Ref.
57	*Heteropyxis canescens*	Stems and root	Column chromatography	1.5 kg	17 mg (0.001%)	225
58	*Durio zibethinus*	Fruit shell	Column chromatography	20 kg	5 mg (0.00002%)	226
59	Hawthorn berries	Berries	Column chromatography	8 kg	4.7 mg (0.0006%)	227
60	*Potentilla chinensis*	Whole plant	CC/MPLC	100 g	5.2 mg (0.05%)	228
61	*Terminalia mollis*[a]	Stem bark	Column chromatography	—	—	229
62	*Myrtus communis*[a]	Leaves	HPLC/HRMS	—	—	230
63	*Solanum melongena* L	Root	Column chromatography	12 kg	6.5 mg (0.005%)	231
64	*Eucalyptus globulus* Wood[a]	Wood	GC-MS	—	—	232
65	*Cochlospermum tinctorium*	Rhizomes	Column chromatography	75 g	75 mg (0.1%)	233
66	*Symplocos lancifolia*	Leaves	HPLC/Column chromatography/prep HPLC	600 g	17 mg (0.002%)	234
67	*Syzygium samarangense*	Areial parts	Column chromatography	—	—	235
68	*Myrica arborea*	Twigs	Column chromatography	1 kg	70 mg (0.007%)	236
69	*Cecropia schreberiana*	Leaves	Column chromatography	590 g	2 mg (0.003%)	237
70	*Premna fulva*	Stalks	Column chromatography			238
71	*Rhododendron hainanense*	Areial parts	Column chromatography	1 kg	2 mg (0.0002)	239
72	*Campsis grandiflora* K. Schum	Flower	Column chromatography	1 kg	33 mg (0.003)	240
73	*Isodon yuennanensis*	Rhizomes	Column chromatography	—	—	241
74	*Momordica cochinchinensis*	Seeds	Column chromatography	50 kg	86 mg (0.001%)	242
75	*Rhodomyrtus tomentosa*	Roots	Column chromatography	—	—	243
76	*Averrhoa carambola*	Fruit	Column chromatography	6.8 kg	13.3 mg (0.001%)	244
77	*Rhododendron collettianum*	Areial parts	Column chromatography	20 kg	15 mg (0.00007%)	245
78	*Datisca cannabina* linn	Whole plant	Column chromatography	15 kg	8.4 mg (0.00005%)	246
79	*Cornus capita*	Leaves	Column chromatography			247

[a] Mixture of arjunolic acid and asiatic acid.

to controls. The study concluded that MOX-HCl-loaded *in situ* gel could serve as an alternative to conventional eye drops, offering extended precorneal retention, enhanced corneal permeability, and improved ocular bioavailability.[168]

In the following section, the various isolation methods of arjunolic acid, its biological activities, and its mechanism of action are presented and thoroughly discussed.

2. Arjunolic acid

Arjunolic acid (AA) (Fig. 3) is a pentacyclic triterpene acid, a major constituent of *T. arjuna* with the IUPAC name 2α,3β,23α-trihydroxy-olean-12-en-28-oic acid. It is reported to exhibit a plethora of biological activities (Fig. 4). It was first isolated by King *et al.* from the heartwood of *T. arjuna*.[5,6,169]

Although arjunolic acid is readily available in *T. arjuna*, it has also been isolated from various other plant sources (Table 2). Along with arjunolic acid, other known reported minor constituents (Fig. 2 and Table 1) of *T. arjuna* include arjunic acid, arjuntenin, baicalein, and quercetin (Fig. 2). Due to the diverse biological profile exhibited by arjunolic acid, many groups have focused their research efforts on this compound.[6,17]

2.1 Isolation of arjunolic acid from *T. arjuna*

The limited number of literature reports on the isolation of arjunolic acid from *T. arjuna* encouraged us to explore novel isolation processes that could furnish arjunolic acid from *T. arjuna* in higher yields.[176] In general, the isolation process adopted by various groups involved the extraction of the plant material with various organic solvents (ethyl acetate, acetone, *etc.*), followed by either chromatographic purification or a recrystallisation process to furnish the pure product.[25,169,170,248,249] However, it was seen that the aforementioned isolation processes were low-yielding (milligram quantities). In another study, Bag *et al.*[250] reported the extraction and separation of arjunolic acid and asiatic acid from the heartwood of *T. arjuna* by employing cumbersome chemical methods involving several synthetic transformations followed by crystallisation. However, Manohar *et al.*[176] were able to efficiently separate arjunolic acid and asiatic acid by a simple flash chromatography method, affording the former in high purity and in large quantities (gram quantities, Table 2, Entry 8). Thus, an efficient process for the isolation of arjunolic acid from the crude plant material was developed in-house by our co-worker Manohar *et al.*, affording arjunolic acid in high yields when compared with the isolated yields reported to date.[176]

3. Biological activities of arjunolic acid

3.1 Cardioprotective activity

Arjunolic acid (AA) has been extensively studied for its cardioprotective effects across various *in vitro* and *in vivo* models. Research by Ghosh *et al.* suggests that doxorubicin-induced cardiac damage results primarily from two mechanisms: first, doxorubicin exposure generates H_2O_2 in myocytes, which

regulates the p53 and p38-JNK signaling pathways in cardiomyocytes; second, activation of p38 and JNK promotes Bax translocation to the mitochondria, disrupting the balance between proapoptotic and antiapoptotic factors. These imbalances trigger mitochondrial permeabilization, leading to cytochrome c release, caspase activation, and cell death. Arjunolic acid supplementation (25 mg kg^{-1} body weight every two days for three treatments) offers protection by detoxifying reactive oxygen species and inhibiting p38 and JNK MAPKs phosphorylation, preventing Bax translocation to the mitochondria and mitochondrial permeabilization.[251]

Sumitra *et al.* further demonstrated the cardioprotective effects of arjunolic acid, showing that it reduces platelet aggregation, coagulation, and myocardial necrosis. In isoproterenol-induced myocardial necrosis, arjunolic acid restored elevated serum enzyme levels (creatine kinase and lactate dehydrogenase) and normalized electrocardiographic parameters, preserving heart architecture pre- and post-isoproterenol exposure.[171]

Trisha *et al.* explored the mechanisms of arjunolic acid and identified its intracellular target in ameliorating hemodynamic load-induced cardiac fibrosis. Results show that AA binds and stabilizes the ligand-binding domain of peroxisome proliferator-activated receptor gamma (PPARγ), increasing its expression during cardiac hypertrophy. In hypertrophic samples, PPARγ knockdown reveals that AA's cardioprotective effects are primarily due to PPARγ agonism. This upregulation of PPARγ inhibits TGF-β signaling by suppressing TAK1 phosphorylation. AA-bound PPARγ interacts with TAK1, masking its kinase domain and decreasing TAK1 phosphorylation, which reduces p38 MAPK and NF-κBp65 activation, ultimately reducing excess collagen synthesis in cardiac hypertrophy.[252]

Prasenjit *et al.* studied the cardioprotective property of arjunolic acid in arsenic-induced oxidative cardiac damage. $NaAsO_2$ exposure (10 mg kg^{-1} body weight) increased arsenic levels in cardiac tissue and reduced antioxidant enzyme activities (superoxide dismutase, catalase, glutathione-*S*-transferase, glutathione reductase, and glutathione peroxidase). Treatment with arjunolic acid (20 mg kg^{-1} body weight for four days before $NaAsO_2$ exposure) protected cardiac tissues by maintaining antioxidant enzyme activities and normalizing oxidative stress markers. Additionally, arjunolic acid prevented arsenic-induced hyperlipidemia and preserved cardiac architecture, as shown in histological studies.[253]

Hassan *et al.* investigated AA's effects on TLR4 downstream signaling in response to lipopolysaccharide (LPS) treatment. LPS exposure upregulated TLR4, MyD88, MAPK, JNK, and NF-κB markers (2–6 times higher than the control), whereas AA treatment downregulated MyD88, NF-κB, p38, and JNK in H9C2 myotubes. AA also decreased TLR4 expression in both H9C2 and C2C12 myotubes, suggesting potential cardioprotective effects through modulation of TLR4 expression.[254]

Gayyar *et al.* highlighted AA's protective effects on sodium nitrite-induced cardiac toxicity. Sodium nitrite increased pro-inflammatory cytokines (TNF-α, IL-1β), C-reactive protein, and caspase activity while reducing anti-inflammatory cytokines (IL-4, IL-10) and cytochrome C oxidase levels. AA treatment reduced pro-inflammatory cytokines and apoptosis markers while increasing anti-inflammatory cytokines and antioxidant enzymes. AA also improved sodium nitrite-induced histopathological changes in cardiomyocytes, suggesting protection against both intrinsic and extrinsic cell death pathways.[255]

Hany *et al.* reported that AA attenuated LPS-induced cardiotoxicity. Pretreatment with AA reduced serum cardiac troponin I, lactate dehydrogenase, and creatine kinase levels in Swiss albino mice. AA pretreatment also increased antioxidant levels, reduced lipid peroxidation, decreased C-reactive protein, and normalized pro- and anti-inflammatory cytokine balance. These findings collectively indicate that AA offers cardioprotection through antioxidant activity, inflammation inhibition, and prevention of cardiac cell death.[256]

3.2 Anti-cancer activity

Arjunolic acid has demonstrated anticancer properties in various *in vitro* and *in vivo* studies. Ramesh *et al.* studied anticancer properties of arjunolic acid. Ehrlich ascites carcinoma (EAC) and Dalton's lymphoma (DAL) cell lines were incubated with different concentrations of arjunolic acid, and the results showed that a 100 μg concentration induced approximately 66% cell death in DAL cells and 70% in EAC cells, primarily through membrane disruption.[257]

Arjunolic acid (AA) was also seen to exhibit significant anticancer activities against MCF-7 and HeLa cell lines, with minimal toxicity observed in normal lymphocytes. Studies have highlighted the self-assembly properties of AA, which contribute to its anticancer effects. Fluorescence-based analyses, such as ROS generation and EtBr/AO and DAPI staining, showed that AA at 50 μg mL^{-1} disrupts redox balance in cancer cells by generating reactive oxygen species. This ROS-induced apoptosis is mediated by regulatory proteins TNF-α and NF-κB, with elevated levels of pro-inflammatory cytokines indicating the involvement of a ROS-driven apoptotic pathway.[258]

In another study reported by Elsherbiny *et al.*,[89] AA showed antitumor effects by enhancing cytotoxicity and apoptosis, partly by blocking TGF-βR1 and modulating inflammatory cytokine levels. In this study, Ehrlich Ascites Carcinoma (EAC) was induced in fifty female Swiss albino mice, and AA was administered at doses of 100 mg kg^{-1} and 250 mg kg^{-1}. AA significantly reduced tumor volume and cell count, decreased cell viability, and increased cytotoxicity in EAC cells. Additionally, AA lowered the levels of TNF-α, IL-1β, TGF-β, TGF-β type I receptor, and latency-associated peptide, while increasing the IL-10 levels in both *in vitro* and *in vivo* conditions.[259]

3.3 Anti-diabetic activity

Arjunolic acid (AA) has been widely studied for its antidiabetic effects across several models. Prasenjit *et al.* investigated AA's prophylactic effects against streptozotocin (STZ)-induced diabetes in the pancreatic tissue of Swiss albino rats. In this study, it was observed that STZ administration (65 mg kg^{-1} body weight *via* tail vein) increased reactive oxygen and nitrogen species (ROS and RNS) in pancreatic tissue. This oxidative stress reduced intracellular antioxidant defense, heightened lipid

peroxidation, protein carbonylation, serum glucose, and TNF-α levels. The signaling pathway analysis showed that STZ activated phospho-ERK1/2, phospho-p38, and NF-κB, and disrupted mitochondrial transmembrane potential, causing cytochrome c release and caspase-3 activation without significantly affecting total ERK1/2 and p38 levels. AA treatment (20 mg kg^{-1} body weight, orally), both before and after STZ administration, effectively mitigated these adverse effects by reducing excessive ROS and RNS formation and down-regulating phospho-ERK1/2, phospho-p38, NF-κB, and mitochondria-dependent apoptosis pathways.[260]

AA's protective effects on hyperglycaemia-induced liver dysfunction were evaluated in experimental rats with type 1 hyperglycaemia induced by STZ. AA, administered orally at 20 mg kg^{-1} before and after diabetes induction, was compared to an insulin-treated positive control. Hyperglycaemia led to body weight loss, reduced serum insulin, increased HbA1C, and elevated advanced glycation end products (AGEs). Markers of liver dysfunction included raised serum alanine transaminase (ALT), alkaline phosphatase (ALP), ROS, RNS, lipid peroxidation, and oxidative DNA damage (8-OHdG/2-dG ratio) along with decreased GSH content and antioxidant defenses. Hyperglycaemia also triggered iNOS, IκBα/NF-κB, and MAPK pathways and mitochondrial signals, which promoted apoptotic cell death. Increased PARP expression, NAD and ATP depletion, and DNA fragmentation in liver tissue confirmed apoptosis. Immunofluorescence with anti-caspase-3 and anti-Apaf-1, DAPI/PI staining, DNA laddering, and FACS analysis corroborated apoptotic death. Histology supported these findings, and AA treatment reduced diabetic liver complications, apoptosis, ROS, RNS, HbA1C, AGEs, and PARP-mediated DNA damage, highlighting AA's potential in diabetic care.[261]

Gonçalves-Neto *et al.* examined whether AA could offset dexamethasone (DEX)-induced glucose imbalance in adult Wistar rats. Groups included vehicle-treated (Ctrl), DEX-treated (1 mg kg^{-1} body weight intraperitoneally for 5 days) (DEX), AA-treated (30 mg kg^{-1} by oral gavage twice daily) (AA s), AA plus DEX (AA DEX), and AA following DEX (DEX AA). AA treatment significantly improved glucose intolerance when administered before and during DEX (AA DEX) but did not ameliorate it when given after (DEX AA). AA failed to reduce the DEX-induced rise in hepatic glycogen and triacylglycerol, and prolonged AA with DEX increased hepatic steatosis. Liver function and oxidative stress markers were not notably altered among groups, suggesting that AA could partly prevent DEX-induced glucose intolerance but was less effective after DEX initiation.[262]

The antidiabetic potential of AA isolated from *T. arjuna* was tested in type 2 diabetic Sprague Dawley rats, with T2DM induced *via* a single STZ-nicotinamide injection. After 10 days, fasting and random blood glucose, body weight, food and water intake, serum C-peptide, insulin, and glycated haemoglobin (HbA1c) levels confirmed T2DM development. Over four weeks, AA (25 and 50 mg kg^{-1} day^{-1}) significantly normalized fasting and random glucose, restored body weight, controlled excessive eating and drinking, and improved glucose tolerance. AA also reduced HbA1c, total cholesterol (TC), triglycerides (TG), and LDL levels, while raising HDL slightly. Serum and pancreatic insulin and C-peptide levels increased with AA, while GDF-15 levels were stable, and AA lowered serum and pancreatic pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6, in a dose-dependent manner.[170]

In another study, AA isolated from *T. arjuna* selectively inhibited glucagon secretion in palmitate-induced αTC1-6 cells and isolated islets, improving hyperglycaemia and pancreatic islet morphology in STZ-induced type 2 diabetic mice. AA's selective inhibition of α-cell glucagon secretion involved ephrin-A1 and EphA4 interaction, which activated the PI3K and Akt pathways, suggesting AA as a promising therapeutic agent for T2DM.[263]

In an STZ-induced diabetic model, AA dosed at 10 and 30 mg kg^{-1} orally over ten weeks was examined for its effect on retinal damage from diabetic retinopathy (DR). H_2O_2-induced ARPE-19 cells were used to assess anti-apoptotic and antioxidant effects. The results showed that AA reduced STZ-induced weight loss, increased retinal thickness and nuclei, and upregulated HO-1 protein levels *in vitro* and *in vivo*. AA protected retinal cells from apoptosis *via* the AMPK-mTOR-regulated autophagy pathway, with dorsomorphin dihydrochloride blocking AA's anti-apoptotic effects, indicating AA's potential as a treatment for diabetic retinal oxidative stress and inflammation.[264]

AA's effects on insulin signaling and TLR-4-Wnt crosstalk in the pancreas of type 2 diabetic rats were investigated by Khurram *et al.* using histology, immunohistochemistry, and RT-PCR. AA treatment reversed T2DM-induced pancreatic apoptosis and necrosis, reduced TLR-4, MyD88, NF-κB, p-JNK, and Wnt/β-catenin levels by inhibiting TLR-4/MyD88 and Wnt signaling, while IRS-1, PI3K, and pAkt were upregulated through NF-κB and β-catenin crosstalk alteration. These findings indicate AA's potential as a therapeutic agent for T2DM-associated meta-inflammation.[265]

3.4 Antioxidant activity

Arjunolic acid is well-documented for its antioxidant activity. It plays an important role in maintaining levels of key antioxidant enzymes, such as catalase (CAT), glutathione-*S*-transferase (GST), glutathione reductase (GR), glutathione peroxidase (GPx), and superoxide dismutase (SOD), along with cellular metabolites such as reduced glutathione (GSH) and oxidized glutathione (GSSG), thereby reducing oxidative stress.

Ramesh *et al.* evaluated the antioxidant properties of arjunolic acid (AA) using four different *in vitro* methods: beta-carotene bleaching assay, DPPH radical scavenging assay, reducing power assay, and hydroxyl radical scavenging assay. The findings were compared with those of standard antioxidants, including ascorbic acid, butylated hydroxytoluene (BHT), and catechin. All four assays confirmed the antioxidant potential of AA, though it showed slightly lower efficacy than the standards.[266]

Maity *et al.* assessed the protective effect of arjunolic acid against arsenic-induced oxidative stress and reproductive dysfunction in female Wistar rats. Sodium arsenite (10 mg kg^{-1}) was administered along with arjunolic acid (10 mg kg^{-1}) for two estrous cycles. Electrozymographic analysis indicated that arjunolic acid co-treatment reduced arsenic-induced ROS production in uterine tissue by enhancing endogenous antioxidant enzyme

activities. Arjunolic acid also helped protect against DNA damage, necrosis, and ovarian and uterine tissue damage in arsenic-treated rats by promoting ovarian steroidogenesis. These protective mechanisms may be related to an enhanced antioxidant defense system, partly facilitated by the elimination of arsenic *via* the *S*-adenosyl methionine pathway, where levels of vitamin B12, folic acid, and homocysteine play crucial roles.[267]

Sinha *et al.* investigated the preventive effects of arjunolic acid on arsenic-induced oxidative damage in the murine brain. Sodium arsenite was used as the arsenic source. The *in vitro* free-radical scavenging activity and *in vivo* antioxidant power of arjunolic acid were assessed using the 2,2-diphenyl-1-picryl hydrazyl (DPPH) radical scavenging and ferric reducing/antioxidant assays, respectively. Oral administration of sodium arsenite (10 mg kg^{-1}) for two days significantly reduced the activity of antioxidant enzymes, including CAT, GST, GR, SOD, and GPx, as well as cellular metabolites, such as reduced glutathione and total thiols, while increasing oxidized glutathione levels. Lipid peroxidation products and protein carbonyl content were also elevated. Treatment with arjunolic acid (20 mg kg^{-1}) for four days before arsenic exposure nearly normalized these levels. Histological findings supported these biochemical results, showing that arjunolic acid mitigates arsenic-induced oxidative damage in the brain. The effects of vitamin C were included as a positive control. Overall, the results suggest that arjunolic acid can protect against arsenic-induced oxidative damage in the brain, likely due to its antioxidant properties.[268]

Arsenic-induced tissue damage is a major concern, particularly because oxidative stress and impaired antioxidant defense are primary causes of arsenic toxicity, which can lead to reproductive failure. Prasenjit *et al.* examined the protective role of arjunolic acid, isolated from *T. arjuna* bark, against arsenic-induced testicular damage in mice. Arsenic administration (10 mg kg^{-1}) over two days significantly reduced antioxidant enzyme activity and cellular metabolite levels, while increasing testicular arsenic content, lipid peroxidation, protein carbonylation, and glutathione disulfide (GSSG) levels. Arsenic exposure also caused degeneration in the seminiferous tubules, leading to necrosis and spermatocyte detachment. Pretreatment with arjunolic acid (20 mg kg^{-1}) for four days helped prevent oxidative stress and structural damage in the testes. Arjunolic acid demonstrated both *in vitro* free radical scavenging activity and *in vivo* antioxidant efficacy. Overall, the study suggests that arjunolic acid's antioxidant properties help prevent arsenic-induced testicular toxicity.[269]

In another study, rats pretreated with arjunolic acid showed significant reductions in neurological deficits and infarct size. Arjunolic acid mitigated ischemia/reperfusion (I/R)-induced neuronal damage by regulating levels of malondialdehyde (MDA), reduced glutathione (GSH), nitric oxide (NO), protein carbonyl content, and mitochondria-generated reactive oxygen species (ROS). It also maintained the activities of Na^+-K^+ ATPase, SOD, CAT, GPx, and GR enzymes, effectively preventing I/R-induced cerebral oxidative damage due to its antioxidant potential.[270]

Sumitra *et al.* examined the modulation of neutrophil function and ROS generation by arjunolic acid *in vitro*. Neutrophils were isolated from normal and myocardial infarction (MI) mice to evaluate AA's efficacy in reducing oxidative stress. Stimulation of neutrophils with phorbol-12-myristate-13-acetate (PMA) resulted in an oxidative burst of superoxide anions (O_2^-) and increased release of lysosomal enzymes. Treatment with arjunolic acid significantly inhibited phosphorylation of p47phox and ERK in both stimulated control and MI neutrophils, reduced oxidative phosphorylation activity, and lowered intracellular oxidative stress. This study highlights potential targets for arjunolic acid in ROS regulation through the MAPK pathway in neutrophils.[271]

Prasenjit *et al.* investigated the benefits of arjunolic acid in modulating cytokine levels and oxidative stress signaling pathways in the spleen under hyperglycaemic conditions. Diabetes was induced by streptozotocin (STZ) injection (70 mg kg^{-1}), which increased IL-2 and IFN-γ levels and decreased TNF-α in diabetic animals. Hyperglycaemia was associated with elevated production of intracellular reactive intermediates, lipid peroxidation, and protein carbonylation, leading to reduced antioxidant defense. Increased expression of phosphorylated p65, its inhibitor phospho IκBα, and phosphorylated MAPKs was also observed in diabetic spleen tissue. Studies on isolated splenocytes showed mitochondrial membrane potential disruption, cytochrome c release, and caspase 3 activation, leading to apoptotic cell death. Histological examination indicated a depletion of white pulp, consistent with reduced immune response.[272]

3.5 Hepatoprotective activity

The hepatoprotective properties of arjunolic acid have been documented by multiple studies.[6] Prasenjit *et al.* assessed arjunolic acid for its protective effects against arsenic-induced oxidative stress in mouse liver tissue. Administering sodium arsenite (10 mg kg^{-1} body weight for two days) notably decreased the activity of antioxidant enzymes—superoxide dismutase, catalase, glutathione-*S*-transferase, glutathione reductase, and glutathione peroxidase—and depleted reduced glutathione and total thiols. It also elevated the levels of serum markers (alanine transaminase and alkaline phosphatase), DNA fragmentation, protein carbonylation, lipid peroxidation products, and oxidized glutathione. Arjunolic acid, known for its *in vitro* radical-scavenging and *in vivo* antioxidant properties, demonstrated protective effects when administered at 20 mg kg^{-1} for four days before arsenic exposure. This pretreatment normalized antioxidant enzyme activities and minimized tissue damage. Histology confirmed reduced liver necrosis with arjunolic acid compared to arsenic alone. Vitamin C served as a positive control, reinforcing arjunolic acid's role in reducing arsenic-induced liver oxidative stress.[249]

Additionally, this study investigated arjunolic acid's potential to protect against acetaminophen (APAP)-induced acute liver toxicity. Exposure to a hepatotoxic APAP dose (700 mg kg^{-1}) increased oxidative stress biomarkers, reactive oxygen species (ROS), and cell death. Pretreatment with arjunolic acid (80 mg kg^{-1}) provided significant liver protection, preventing glutathione depletion and reducing APAP metabolite formation, without affecting hepatic glutathione levels. The findings suggest that arjunolic acid inhibits APAP bioactivation by

cytochrome P450 and reduces APAP-induced JNK and Bcl-2 phosphorylation, thus preventing mitochondrial damage.[175]

In another model, arjunolic acid was tested for its protective effects against arsenic trioxide (ATO)-induced oxidative stress in mouse liver and kidney tissues. Administering ATO (30 mg kg^{-1} day^{-1} for eight weeks) elevated serum markers, ROS, and disrupted the prooxidant-antioxidant balance, triggering apoptotic pathways. Post-treatment with arjunolic acid (20 mg kg^{-1} for four days) mitigated oxidative stress and apoptosis markers, including mitochondrial membrane potential loss, caspase activation, and cytochrome c release.[273]

In a study on cisplatin-induced liver toxicity, arjunolic acid demonstrated hepatoprotective effects by reducing oxidative stress, inflammation, and apoptosis. Rats pretreated with arjunolic acid (20 mg kg^{-1} for 10 days) showed improved liver function, histology, and suppressed malondialdehyde and nitric oxide levels. Arjunolic acid significantly enhanced antioxidant enzyme activities, reduced tumor necrosis factor α, and decreased caspase-3 expression.[274]

Arjunolic acid also reduced lipid accumulation in free fatty acid (FFA)-challenged hepatocytes without toxicity. *In vivo*, arjunolic acid reduced adiposity, hepatic inflammation, and lipid disorders in the non-alcoholic fatty liver disease (NAFLD) model, activating Sirt1/AMPK pathways, enhancing autophagy, and restoring gut barrier integrity.[275]

Finally, in NAFLD models, arjunolic acid showed promising results by reducing triglyceride accumulation, ALT, and AST levels. *In vivo*, it lowered liver enzyme markers and modified PPAR and FXR expression, indicating reduced liver steatosis and inflammation. Collectively, these studies suggest arjunolic acid as a promising agent for liver protection across various hepatic damage models due to its antioxidant, anti-inflammatory, and anti-apoptotic effects.[172]

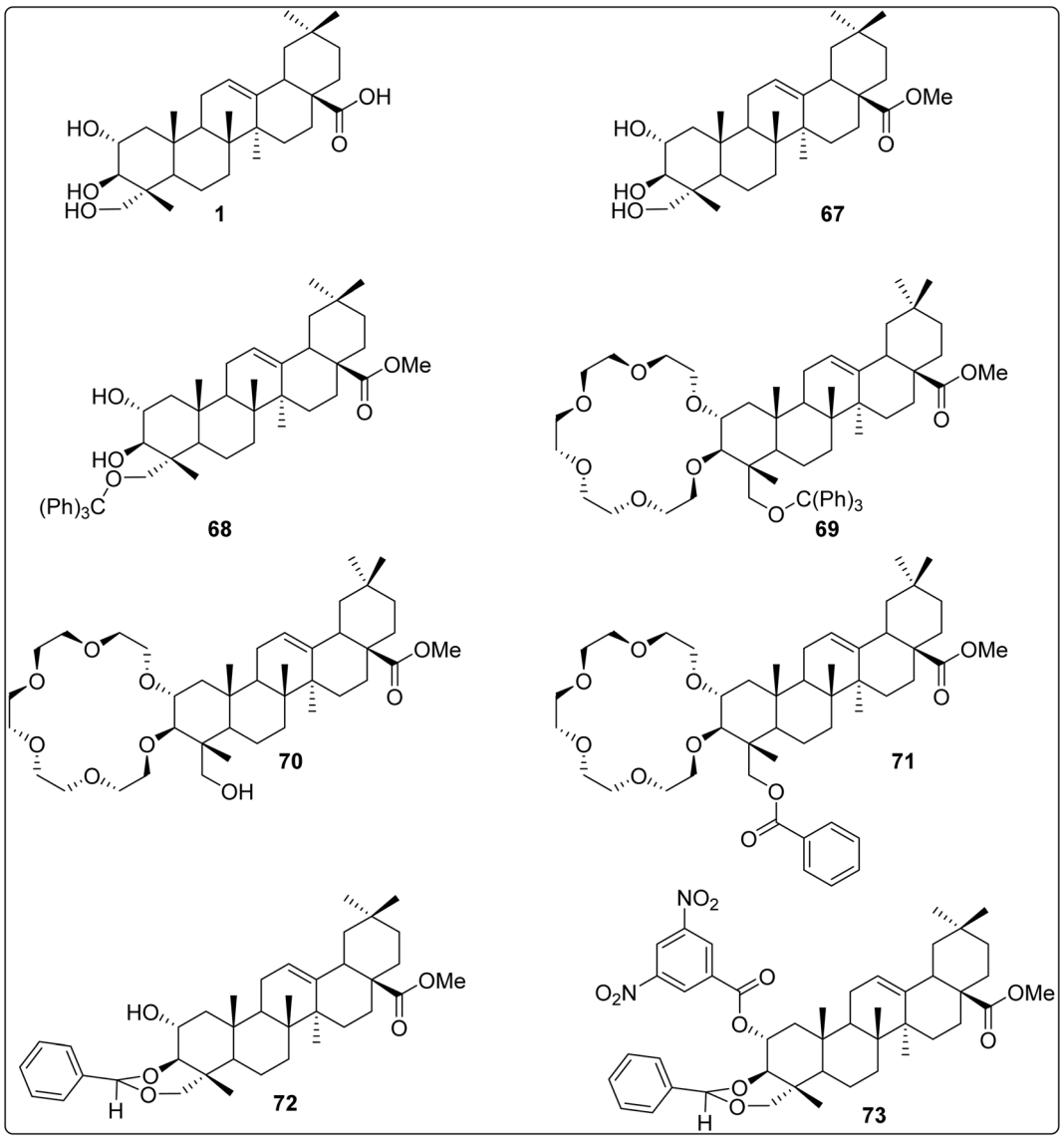

Fig. 5 Arjunolic acid analogues synthesized by Bag *et al.*[285,286,291]

3.6 Anti-inflammatory activity

Arjunolic acid has been widely studied for its anti-inflammatory properties. The anti-arthritic effects of arjunolic acid were evaluated in a rat model of arthritis induced by complete Freund's adjuvant (CFA). Arthritis was induced in male Sprague Dawley rats through an intradermal injection of 0.1 mL CFA into the right footpad. Following arthritis induction, arjunolic acid was administered orally at doses of 40 and 80 mg kg^{-1} once daily for 25 consecutive days. Indomethacin, a reference drug, was given at 3 mg kg^{-1} twice weekly for the same duration. Standard procedures were used to assess paw swelling, serum haematology, antioxidant enzymes, inflammatory mediators, and histopathology. The results showed that arjunolic acid significantly ($p < 0.01$) reduced paw swelling and weight loss in arthritic rats. It also lowered malondialdehyde (MDA) levels, spleen index, and thymus index, while enhancing the activities of superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx). Furthermore, arjunolic acid downregulated TNF-α, IL-1β, and IL-6 serum levels ($p < 0.01$), improving haematological and histopathological changes in CFA-induced arthritis due to its anti-inflammatory effects.[276]

Atopic dermatitis (AD), a chronic, pruritic, eczematous skin disorder associated with allergic inflammation, involves oxidative stress and immune imbalance. The anti-pruritic effects of oral arjunolic acid (AA) were studied in a mouse model of AD induced by 2,4-dinitrochlorobenzene (DNCB). Mice were treated with DNCB on their ears and shaved dorsal skin to induce AD-like symptoms, followed by oral administration of AA at 250 mg kg^{-1} for three weeks. The results indicated that AA significantly improved AD symptoms, reducing skin lesions, dermatitis scores, ear thickness, and scratching behaviour. AA also decreased reactive oxygen species and modulated inflammatory markers, lowering serum TNF-α, IL-6, IgE, and caspase-3 while maintaining IL-4 and IL-10 levels, thus mitigating DNCB-induced AD symptoms.[277]

Zining *et al.* investigated arjunolic acid's effect on a Crohn's disease (CD) model. CD was simulated in IL-10 knockout mice, with arjunolic acid's impact assessed through weight monitoring, histopathology, and intestinal barrier function. Arjunolic acid improved colitis symptoms, reducing weight loss, inflammation scores, and enhancing intestinal permeability. AA also inhibited apoptosis in intestinal epithelial cells by reducing Bax and C-caspase-3 levels. Mechanistic analysis revealed that AA suppressed TLR4 signaling and altered gut microbiome composition, increasing short-chain fatty acid-producing bacteria. Fecal transplantation from AA-treated mice alleviated CD-like colitis in recipient mice, highlighting AA's potential to inhibit key inflammatory pathways and promote gut microbiota balance in CD therapy.[278]

Edozie *et al.* evaluated the protective effects of arjunolic acid on fluoxetine (FXT)-induced testicular dysfunction in male rats. Thirty-six rats were assigned to six groups and treated with combinations of saline, arjunolic acid (1.0 or 2.0 mg kg^{-1}), fluoxetine (10 mg kg^{-1}), or fluoxetine plus arjunolic acid. The results showed that FXT treatment disrupted testicular steroidogenic enzymes (3β-HSD and 17β-HSD), ATPase enzymes, and testicular structure. FXT also increased oxidative inflammation markers (MDA, MPO, TNF-α, IL-1β, caspase-3, and p53) and promoted apoptosis. Arjunolic acid treatment counteracted these effects, restoring steroidogenic enzyme activity, improving testicular structure, and increasing antioxidant levels (SOD, CAT, GSH) while reducing oxidative stress and inflammation.[279]

Ying *et al.* investigated the effects of arjunolic acid on depression and its potential mechanisms. *In vivo* and *in vitro* models were established by administering intraperitoneal injections of lipopolysaccharide (LPS) to mice and stimulating BV2 microglia with LPS. Behavioral tests, H&E staining, and

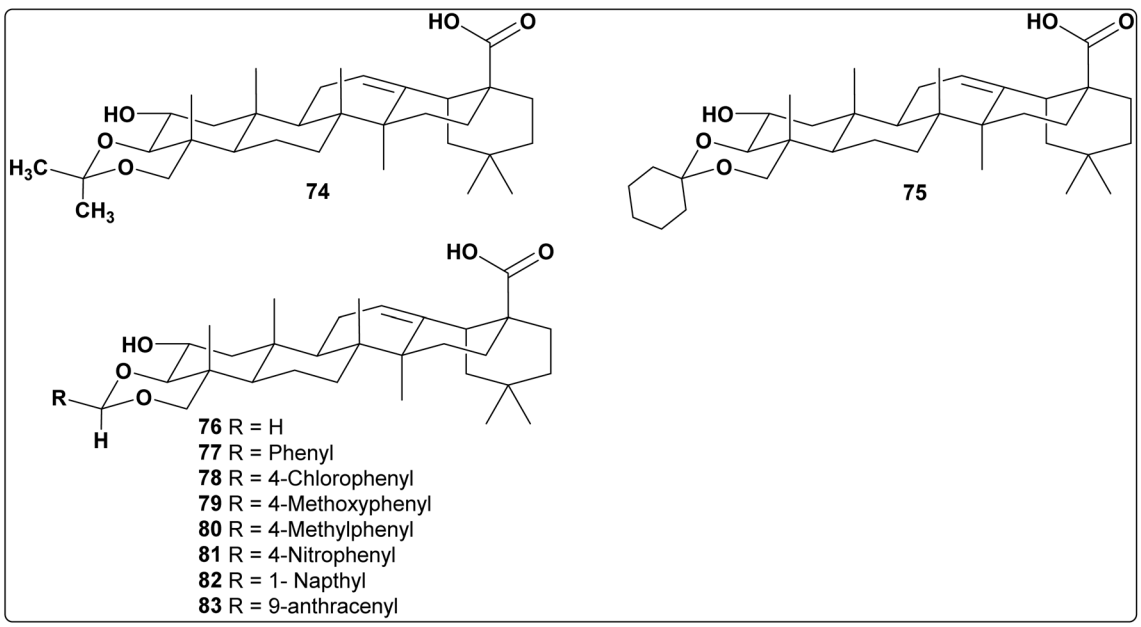

Fig. 6 Aromatic and aliphatic acetals/ketals of arjunolic acid synthesized by Bag *et al.*[292]

ELISA were conducted to assess arjunolic acid's effect on depression, while RT-qPCR, immunofluorescence, molecular docking, and Western blot analyses were performed to explore the molecular mechanisms. Arjunolic acid significantly improved depressive behaviors in LPS-treated mice, elevated BDNF and 5-HT levels in the hippocampus, decreased iNOS + IBA1 + cells, and increased Arg1 + IBA1 + positive cells in the brain. Furthermore, arjunolic acid facilitated the polarization of BV2 microglia from the M1 to M2 phenotype. Notably, DARTS, CETSA, and molecular docking techniques identified SIRT1 as a target of arjunolic acid. Inhibition of SIRT1 with EX-527 blocked arjunolic acid's effects on reducing LPS-induced depressive behavior and promoted M2 microglia polarization. Additionally, arjunolic acid activated AMPK and reduced Notch1 expression; however, inhibiting AMPK weakened its effect on Notch1 downregulation. This study revealed that

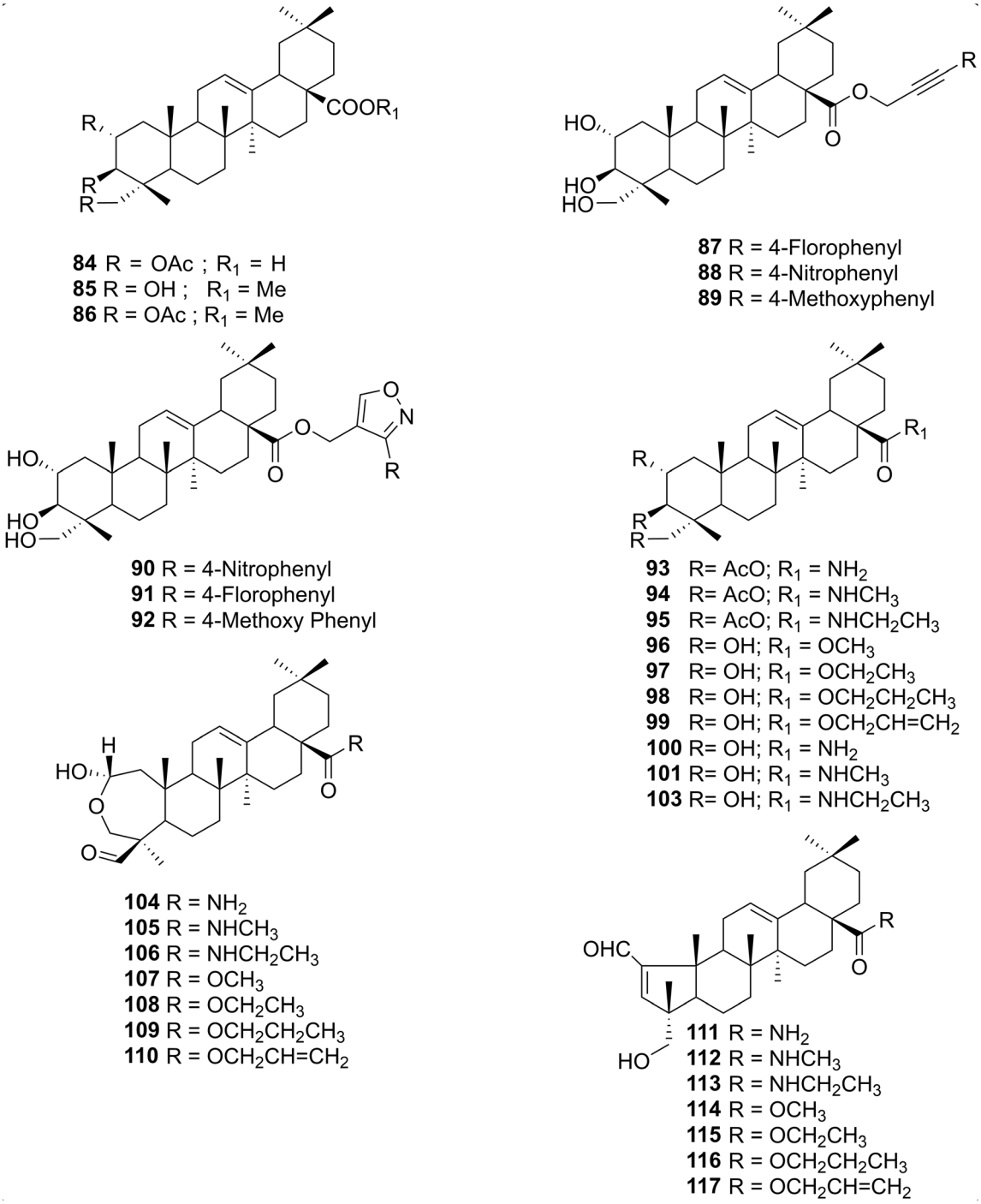

Fig. 7 Arjunolic acid analogues synthesized by various groups exhibiting anti-oxidant, anti-cancer, anti-viral, and α-glucosidase inhibitory activities.[9,233,288,289]

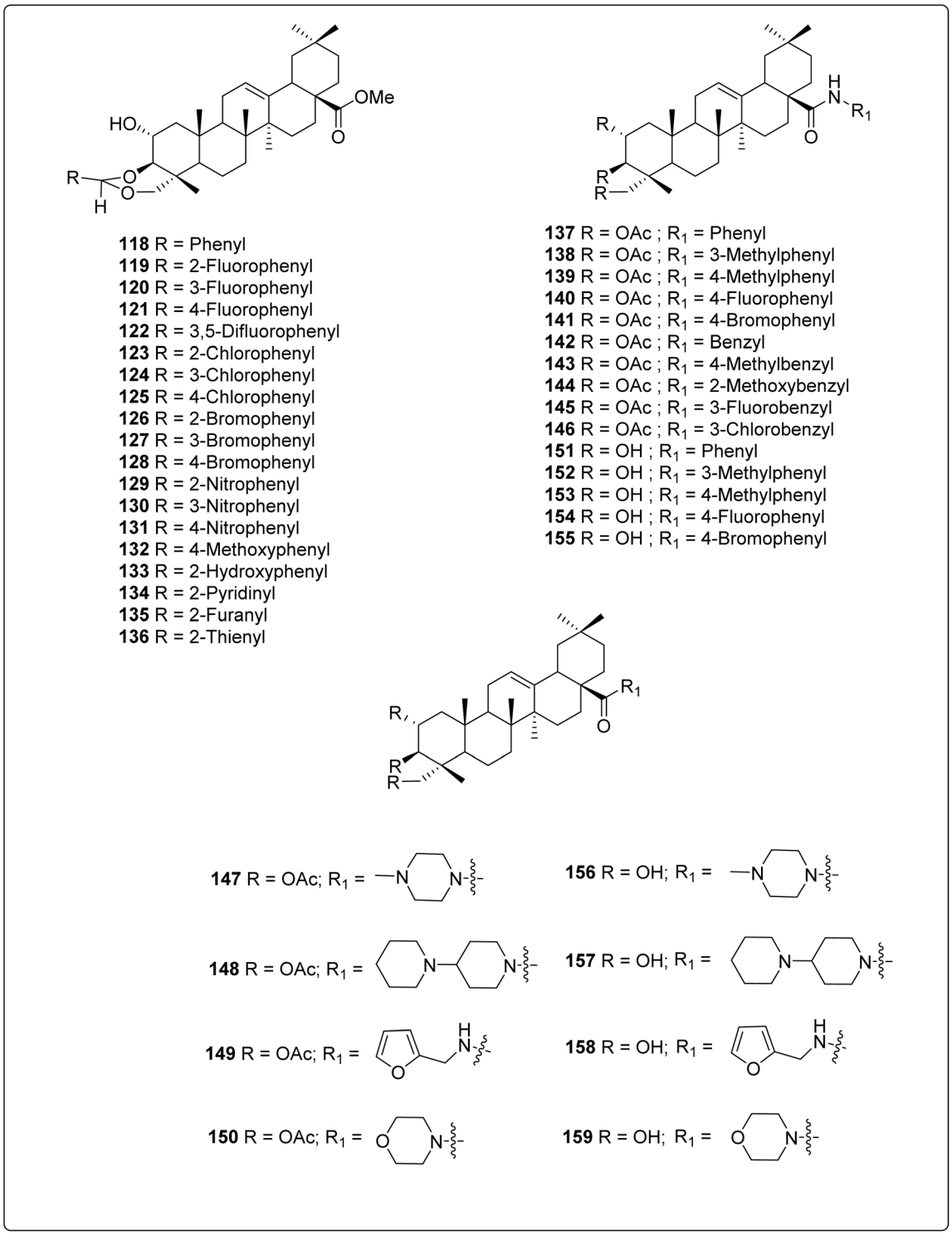

Fig. 8 Arjunolic acid derivatives synthesized by Manohar *et al.,* exhibiting anti-cancer activities.[7]

arjunolic acid mitigates neuroinflammation by modulating the SIRT1/AMPK/Notch1 signaling pathway, suggesting its potential as an antidepressant agent.[280]

3.7 Anti-asthmatic activity

Arjunolic acid has been reported to exhibit anti-asthmatic properties. In a study with rats, treatment with arjunolic acid at doses of 50 and 100 mg kg^{-1} body weight provided significant protection against mast cell disruption, showing 42% and 33% degranulation, respectively, compared to the standard degranulation level induced by disodium chromoglycate. Additionally, arjunolic acid at these doses offered 49% and 64% protection against histamine challenges and 40% and 51% protection against acetylcholine challenges. These anti-asthmatic effects of

Table 3 Structural modifications leading to various biological activities

Therapeutic action	Rings of arjunolic acid	Modifications
Anti-cancer	A	Selective conversion of hydroxyls (R–OH) attached at C-2, C-3 and C-23 to acetals and acetates
	A	Conversion of the A ring to lactol
	A	Simultaneous conversion of the A ring to a five-membered ring containing an α,β-unsaturated carbonyl moiety, and conversion of the acid (R–COOH) at C-28 to alkyl esters or alkyl amides
	D/E	Selective conversion of acid (R–COOH) at C-28 to amides
Anti-diabetic	D/E	Selective conversion of acid (R–COOH) at C-28 to aryl propargyl esters and isoxazole carbinol esters
Anti-viral	A	Simultaneous conversion of hydroxyls (R–OH) attached at C-2, C-3 and C-23 to acetates
	D/E	Selective conversion of acid (R–COOH) at C-28 to methyl ester
Anti-oxidant	A	Selective conversion of hydroxyls (R–OH) attached at C-2, C-3 and C-23 to acetates

arjunolic acid may be attributed to its ability to stabilize mast cells and inhibit the release of histamine and acetylcholine in response to antigens.[281]

3.8 Anti-microbial activity

Arjunolic acid has demonstrated moderate antimicrobial activity. Isolated from the leaves of *Syzygium guineense*, arjunolic acid exhibited antibacterial effects against *Bacillus subtilis* (0.5 μg per spot), *Escherichia coli* (3 μg per spot), and *Shigella sonnei* (30 μg per spot).[282] It also showed inhibitory activity against *Cryptococcus neoformans*, with an IC_{50} of 20 μg mL^{-1}, and demonstrated significant antibacterial activity against *Brucella melitensis*, with a zone of inhibition of 9 mm and a minimum inhibitory concentration (MIC) of 30 μg mL.[283,284] Furthermore, a mixture of arjunolic acid and asiatic acid exhibited moderate antifungal effects against *Candida albicans* and *Candida parapsilosis*.[229]

3.9 Insecticidal activity

Bhakuni *et al.* identified the insecticidal activity of arjunolic acid. Arjunolic acid, isolated from the stem of *Cornus capitata* (Wall. ex Roxb.) showed significant inhibitory effects on the fourth instar larvae of *Spilarctia obliqua*. A dose-dependent effect was observed, with optimal concentrations for reducing larval feeding and growth found to be 617 ppm and 666 ppm, respectively.[247]

3.10 Physicochemical properties

Bag *et al.* studied the potential of arjunolic acid as a robust and functional molecular framework suitable for creating nanoscale supramolecular architectures and nanomaterials. This nano-sized triterpenoid demonstrated effective gelation of various organic solvents (methanol, ethanol, propanol, butanol, dichloromethane, chloroform, cyclohexane, benzene, cyclohexanone, diethylene glycol, and triethylene glycol) at low concentrations. In these solvents, low molecular weight gelator molecules self-assembled to form nanofibers, creating a fibrous network that restricted solvent movement, resulting in gel formation.[285] Arjunolic acid also exhibited hierarchical self-assembly in aqueous solutions, forming vesicular structures on nano-to micrometer scales that contribute to gel formation and have proven effective for encapsulating and releasing anticancer drugs such as doxorubicin at physiological pH.

Bag *et al.* also highlighted the self-assembly properties of sodium and potassium salts of arjunolic acid in water and aliphatic alcohols, showing that, at lower concentrations, the molecules form vesicular structures, while, at higher concentrations, they transition into large fibrillar assemblies to create stable gels. These vesicular assemblies are further utilized for the controlled release of various set fluorophores, including doxorubicin, at physiological pH.[286,287]

4. Analogues of arjunolic acid and their biological activities

Diverse research groups[7,9,233,288,289] have subjected arjunolic acid to semi-synthetic modifications by carrying out either selective or simultaneous transformations to various rings and functional groups present in arjunolic acid.

Bag *et al.* first reported the synthesis of an 18-crown-6 methyl ester derivative of arjunolic acid. Arjunolic acid was converted into its methyl ester (**67**). The primary hydroxy group of compounds (**67**) was protected using trityl chloride to yield compound (**68**). This compound was further reacted with sodium hydride and pentaethyleneglycol ditosylate in dry THF to yield 23-[(triphenylmethyl)oxy]– 28-(methoxycarbonyl)-arjuna-18-crown-6 (**69**). This compound was further reacted with dichloro acetic acid to obtain compound (**70**), which was further treated with benzoyl chloride to yield the final product (**71**, Fig. 5). In the same study this group also reported the synthesis of benzylidene derivatives (**72–73**, Fig. 5) prepared by reacting arjunolic acid methyl ester with benzaldehyde in the presence of perchloric acid as a catalyst. The hydroxy group at the 2-position of the compound was esterified with 3,5-dinitrobenzoyl chloride, and these derivatives were examined for organogelator properties in various organic solvents.[285,290]

Subsequently Bag's team synthesized ten aliphatic and aromatic acetals and ketals of arjunolic acid (Fig. 6) and studied their self-assembly properties in diverse organic solvents. Except for the *p*-nitrobenzylidene derivative, these ketals, at low concentrations, formed gel-like dispersions in several organic solvents. Using optical, electron, and atomic-force microscopies, the morphologies were found to consist of fibrillar networks and vesicles capable of entrapping 5(6)-carboxyfluorescein. X-ray diffractograms showed that the fibrillar structures were crystalline. Additionally, a charge–transfer complex was formed from a 1 : 1 mixture of ketal derivatives with electron-donating and electron-accepting groups, and the fibrillar network of the 9-anthrylidene derivative dimerized under irradiation. This work demonstrates that minor structural variations in the ketals significantly influence their aggregation pathways.[292]

Reddy *et al.* reported the synthesis and HPLC validation of acetylated arjunolic acid (**84**, Fig. 7), which showed higher antioxidant activity than arjunolic acid, BHT, and vitamin E, as measured by the thiobarbituric acid method (TBA).[289]

Diallo and co-workers reported the synthesis of the triacetate of arjunolic acid and its methyl ester. Compound **1** was treated with acetic anhydride and pyridine at room temperature for 12 hours to yield compound **84**. Methylation of **1** and **84** was achieved by treating them with diazomethane in diethyl ether at room temperature to yield compounds **85** and **86** (Fig. 7). These compounds were tested for Epstein–Barr virus (EBV) inhibition and further assessed in a two-stage carcinogenesis assay in

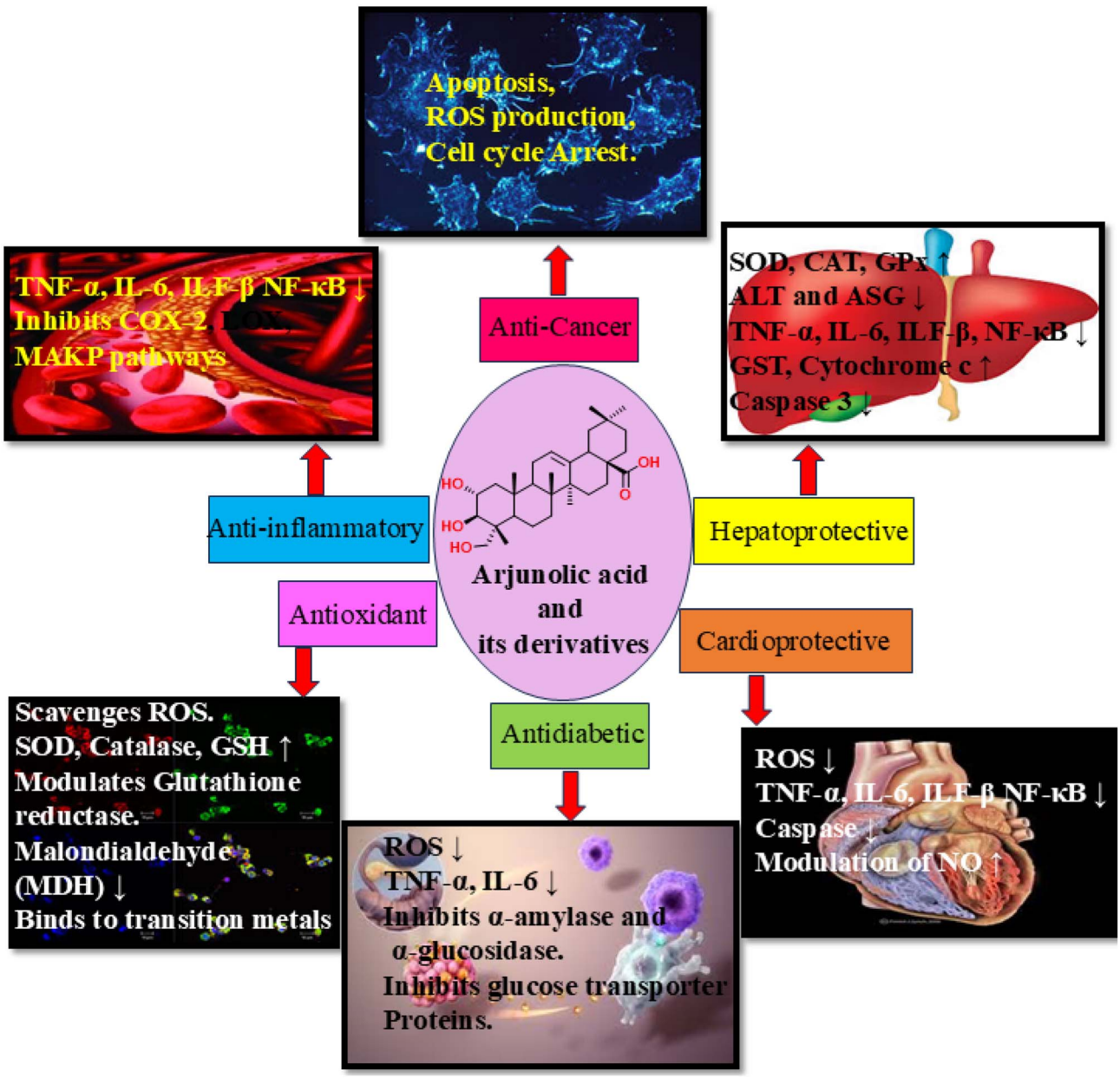

Fig. 9 Mechanism of arjunolic acid and its derivatives for various biological activities.

mouse skin. The results indicated that mice treated with the triacetate and triacetate methyl ester of arjunolic acid showed delayed papilloma development compared to the controls.[293,294]

Bolatito *et al.* synthesized new phenyl acetylene and isoxazole analogues of arjunolic acid. The acid functional group was converted into the propargyl ester using propargyl bromide. This propargyl ester of arjunolic acid was reacted with substituted aryl iodide in the presence of a palladium catalyst to obtain compounds **87–89**. Simultaneously, this propargyl ester was reacted with various bromoaldoximes to yield compounds **90–92**. These analogues were evaluated for their tyrosinase and alpha-glucosidase inhibitory activity. All the tested analogues showed stronger inhibitory effects than the standard drug acarbose. One compound demonstrated tyrosinase inhibition with an IC_{50} of 14.3 ± 7.6 μM, about three times more potent than kojic acid (IC_{50} of 41.5 ± 1.0 μM). Additionally, compound **89** exhibited significant alpha-glucosidase inhibition activity with an IC_{50} close to that of the standard acarbose (10.4 ± 0.06).[9]

Bruno *et al.* synthesized novel arjunolic acid derivatives containing a five-membered A-ring with an enal moiety, combined with additional modifications of COOH (at C-28) as esters and aliphatic amides. Compounds **93–103** were reacted with $NaIO_4$ at room temperature to yield compounds **104–110**. These derivatives were further treated with acetic acid and piperidine and refluxed in dry benzene before being subjected to reflux with anhydrous magnesium sulphate to yield compounds **111–117**. These derivatives were tested for cytotoxicity on cancer and non-tumor human cell lines, aiming to identify promising compounds. Compound **115** showed the highest selectivity between malignant cells and non-malignant fibroblasts. This compound also induced cell cycle arrest in the G_0/G_1 phase and significantly inhibited the wound closure rate of PANC-1 cancer cells. At a concentration of 0.24 μM, compound **115** synergistically enhanced gemcitabine cytotoxicity and showed no toxicity at lower doses in preliminary pharmacological studies.[8]

Manohar *et al.* synthesized various acetals (**118–136**, Fig. 8) and amides (**137–159**, Fig. 8) of arjunolic acid and evaluated their anticancer properties. All the synthesized compounds (**118–159**) were tested against 60 cancer cell lines, representing nine different cancer types, at the National Cancer Institute (NCI), USA. These acetals and amides of arjunolic acid exhibited significant activity, particularly against colon, leukemia, breast, and melanoma cancer types. From the library of acetals (**118–136**), compounds **119**, **121**, **126**, and **135** demonstrated activity against all nine cancer types, including breast cancers, colon, CNS, leukemia, non-small cell lung cancer, melanoma, ovarian, renal, and prostate cancer. Among these, compound **126** exhibited the most potent IC_{50} value of 1.56 μM against the CT-26 cancer cell line. Further studies on compound **126** revealed that it induces ROS generation, causing cell necrosis by arresting cells in the G_2/M phase of the cell cycle.

Tri-hydroxy amides (**151–155**, Fig. 8) showed greater activity than tri-acetate amides in the series of aniline-substituted amides, Fig. 8. Conversely, in the case of amides derived from heterocyclic amines, tri-acetate amides (**147–150**) were more active compared to tri-hydroxy amides (**156–159**). Substituted benzylamine amides were inactive against all cancer cell lines. Among the amides, compound **147** exhibited the best IC_{50} values, with 1.88 μM against the CT-26 cell line and 0.4 μM against the HCT-116 colon cancer cell line. Further investigations revealed that compound **147** induces apoptosis through ROS generation and arrests cells in the G_0/G_1 phase of the cell cycle. *In vivo* studies also showed that compound **147** inhibited cancer growth in the case of the mouse model.[7]

Analysis of the structure–activity relationship (SAR) and modifications responsible for the therapeutic profile of arjunolic acid derivatives is tabulated in Table 3. These studies could help identify future hits, optimize lead molecules with drug-like properties and support future drug discovery efforts. We have also made efforts to capture the mechanisms of action of biological activities exhibited by arjunolic acid and its derivatives in Fig. 9.

5. Conclusion

In summary, natural products continue to be a constant source of interesting biologically active molecules. *T. arjuna*, a traditional medicinal plant native to the Indian subcontinent, was shown to exhibit several medicinal properties and was thus used in traditional medicine. Arjunolic acid, the major triterpenoid constituent of *T. arjuna*, has been reported to exhibit a plethora of biological activities. The structural amenability of arjunolic acid for diverse modifications has attracted the attention of various research groups, affording semi-synthetic derivatives with interesting therapeutic value. To date, many investigations have focused their research efforts on exploring the multi-therapeutic potential of arjunolic acid and delineating its corresponding mechanism of action. However, the limited reports on arjunolic acid analogues and their corresponding biological profile reveal that its therapeutic potential as a source of new drug leads has not yet been thoroughly explored. The continuous rise in FDA approvals for natural-product-based drugs further augments the need to look at arjunolic acid as a potential new source of natural-product-based drug leads. Hence, natural-product-based drug-discovery programs focused on arjunolic acid would build on the existing armamentarium of desirable molecules with drug-like properties and with a potential for clinical trials.

Author contributions

Manohar Bhujel: methodology, investigation, writing – original draft preparation. Sai Giridhar Sarma Kandanur: conceptualization, methodology, investigation, writing – original draft Preparation. Lakshminath Sripada: conceptualization, supervision, writing – reviewing and editing. Nageswara Rao Golakoti: conceptualization, supervision, writing – reviewing and editing.

Conflicts of interest

Authors M. B., L. S. and N. R. G. have a patent "A Process For Separating Arjunolic Acid And Asiatic Acid From Heartwood of Terminalia Arjuna" pending to the Sri Sathya Sai Institute of

Higher Learning, Prasanthi Nilayam-515134, India. The authors declare no additional conflicts of interest.

Data availability

No primary research results, software or codes have been included, and no new data were generated or analysed as part of this review.

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