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# Systematic Analysis of the Pharmacological Properties of Different Plant Parts of *Madhuca* sp.

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***Abstract***

*Madhuca sp., a perennial tree belonging to the Sapotaceae family, is widely distributed across South and Southeast Asia. It holds considerable value across the food, beverage, and pharmaceutical sectors. The growing interest among cultivators, agronomists, and industry stakeholders stems from the diverse bioactive potential documented across different parts of the plant, including the bark, leaves, seeds, and flowers. Traditional and emerging evidence points to a wide spectrum of pharmacological actions, ranging from antioxidant and antimicrobial effects to anticancer, hepatoprotective, nephroprotective, and neuroprotective properties, positioning the plant as a promising, low-toxicity alternative to synthetic drugs, many of which are limited by adverse effects or the development of resistance. This review consolidates and critically evaluates the existing body of research on the pharmacological properties associated with the various plant parts of Madhuca sp. A structured literature search was conducted through ScienceDirect, PubMed, and the Elicit research tool, initially identifying over a thousand potentially relevant publications. Screening followed the PRISMA framework, with most records excluded based on poor topical relevance or unavailability of full text, ultimately narrowing the pool to twenty-three studies that met the inclusion criteria for detailed analysis. The synthesis reveals part-specific pharmacological trends: bark extracts show the strongest anticancer and antioxidant activity linked to high flavonoid and tannin content; leaves display the broadest range of biological effects, including neuroprotection and antidepressant-like activity; seeds and seed oil are primarily protective against liver and kidney damage, though they also carry the greatest toxicity risk among the plant parts; and flowers exhibit moderate antioxidant, anti-inflammatory, and antimicrobial activity. Notably, all available evidence originates from preclinical, animal, or in vitro models, with no clinical trials conducted in humans to date, underscoring a critical gap that future research should address before therapeutic translation can be considered.*

**Keywords:** Antioxidant activity, antimicrobial activity, plant extraction, anticancer activity, neuroprotection

## INTRODUCTION

*Madhuca* species (predominantly *M. longifolia* and *M. indica*) exhibit a differentiated pharmacological profile across plant parts, as demonstrated by 23 preclinical studies spanning in vitro and in vivo models. Bark extracts show the most potent anticancer and antioxidant activities, with IC50 values as low as 0.012 µg/mL against HCT116 colon cancer cells [1]and DPPH IC50 of 18.86 µg/mL [1], consistent with their high flavonoid (975 mg CE/g) and condensed tannin (980 mg CE/g) content [2]. Bark-derived flavonoid-loaded gold nanoparticles further enhanced anti-melanoma efficacy from 65.15% to 85.15% [3]. Leaf extracts demonstrate the broadest pharmacological versatility, with documented neuroprotective effects in colchicine-induced amnesia (GSH increase, AChE decrease; $P < 0.001$)

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[4] and rotenone-induced Parkinson's disease models (reduced LPO, TNF-α; $P < 0.05$) [5], hepatoprotective activity comparable to silymarin [6], antidepressant effects at 75–750 mg/kg [7], and antimicrobial activity against Multidrug-resistant bacteria (MDR) bacteria (MIC 0.78–1.56 mg/mL) [8]. Seed and seed oil preparations are primarily hepato- and nephroprotective, significantly reducing liver and renal enzyme markers in toxicity models [9, 10], while flower extracts exhibit moderate antioxidant (65–90% DPPH scavenging) [11], anti-inflammatory, and antimicrobial properties [12], along with aphrodisiac effects in poultry [13]. Across all plant parts, the dominant mechanisms involve antioxidant-mediated cytoprotection, suppression of pro-inflammatory cytokines, and Reactive oxygen species (ROS)-mediated apoptosis in cancer models [1, 5, 9]. Acute oral toxicity studies indicate a favorable safety profile, with no adverse effects at doses up to 2000–2500 mg/kg for leaf and seed extracts [9, 14], though a comparative toxicology study in fish ranked intrinsic toxicity as seed > bark > leaf [15]. All evidence derives from preclinical models, and no human clinical data are available. The workflow of systematic analysis is shown in Figure 1. The Elicit-based screening methodology is shown in Figure 2.

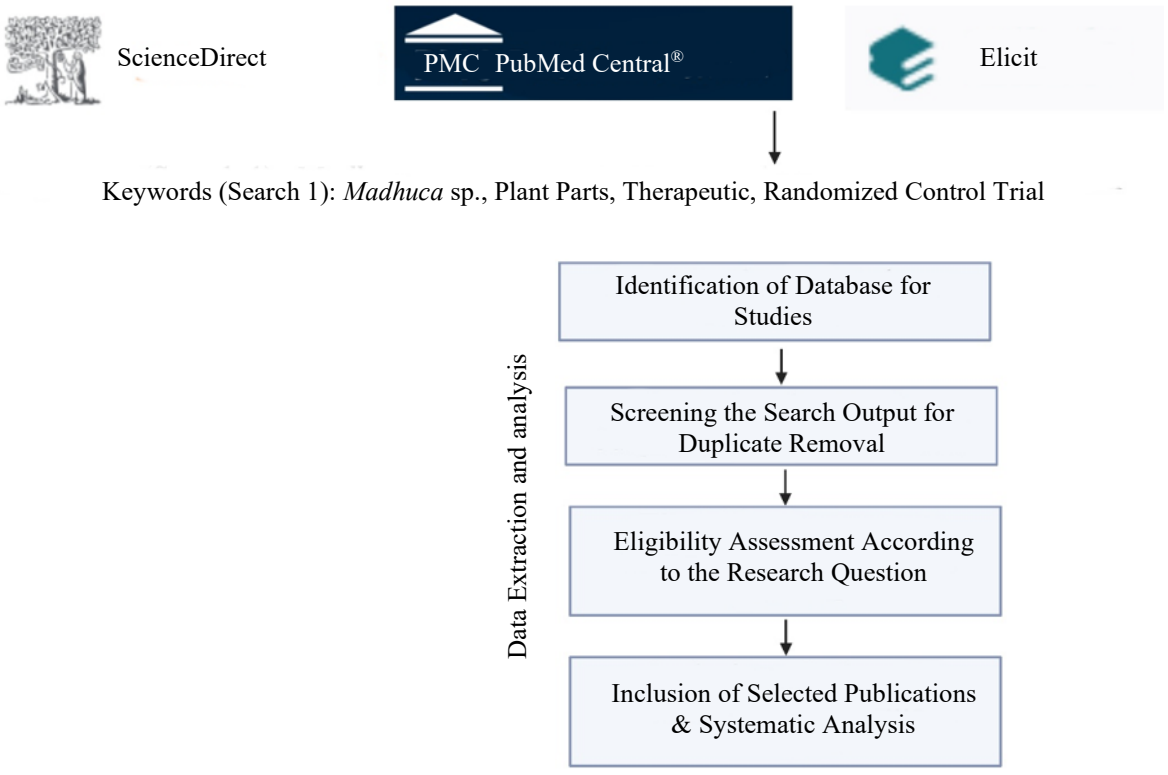


**Figure 1.** Schematic workflow for data screening and selection from different databases and tools.

## RESULTS

### Characteristics of Included Studies

Different plant parts of *Madhuca* sp. exhibit distinct pharmacological strengths: bark is the most potent for anticancer and antioxidant activities due to its high flavonoid and tannin content, leaves are the most pharmacologically versatile with demonstrated neuroprotective, hepatoprotective, antidepressant, and antimicrobial properties, seeds and seed oil are primarily hepato- and nephroprotective but carry the highest intrinsic toxicity, and flowers show moderate antioxidant, anti-inflammatory, and antimicrobial effects.

The 23 included studies encompassed a broad range of pharmacological investigations across multiple *Madhuca* plant parts, species, extraction methods, and experimental designs. Most studies

 

examined *M. longifolia*, with a smaller subset investigating *M. indica* (a taxonomic synonym). Study designs ranged from in vitro cell-based and antimicrobial assays to in vivo animal models using rodents, poultry, and fish. No human clinical trials were identified. Table 1 summarizes the key characteristics of all included studies.

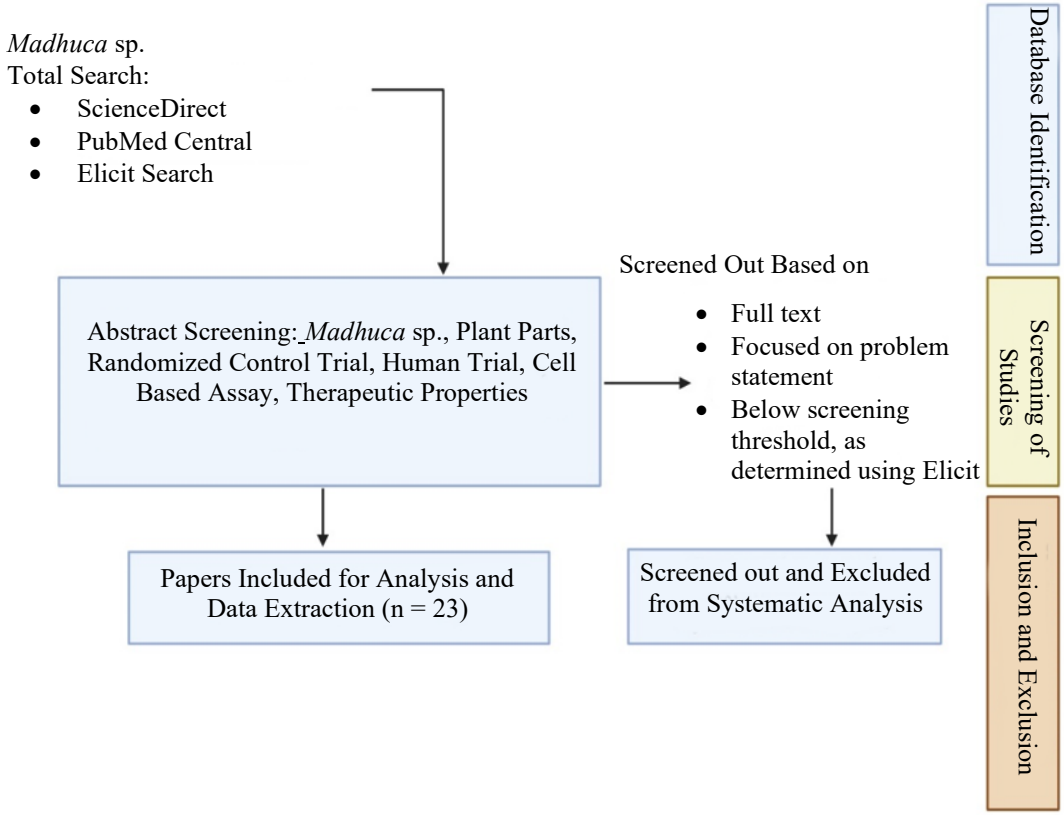


**Figure 2.** Process flow for screening of databases for relevant studies and inclusion and exclusion criteria.

**Table 1.** Systematic analysis of *Madhuca sp.* Plant part, extraction process and study type showing the therapeutic potential of plant extract.

| Study | Full text retrieved | Species | Plant part | Extract/solvent | Study type | Primary activity investigated |
|---|---|---|---|---|---|---|
| Wardhan & Sharma, 2025 | Yes | *M. longifolia* [9] | Seed [9] | Ethanol (Soxhlet) [9] | In vivo (Wistar rats) [9] | Hepatoprotective [9]. |
| Barycka et al., 2026 | Yes | *M. longifolia* [1] | Bark [1] | 70% aqueous ethanol [1] | In vitro (HT-29, HCT116, FHC cell lines) [1] | Anticancer (colon carcinoma) [1]. |
| S. T. et al., 2021 | Yes | *M. longifolia* [16] | Leaf and bark [16] | Methanol, ethanol, aqueous [16] | In vitro (disc diffusion) [16] | Antibacterial [16]. |
| Kendre & Wakte, 2022 | Yes | *M. longifolia* [17] | Leaves [17] | Aqueous, hydroalcoholic, ethanolic [17] | In vitro (MCF-7 cell line) [17] | Anticancer (breast cancer) [17]. |
| Simon et al., 2020 | Yes | *M. longifolia* [6] | Leaf [6] | Aqueous [6] | In vivo (Wistar rats, 10 and 15 days) [6] | Hepato-/nephro-/gastroprotective [6]. |
| Bala et al., 2025 | Yes | *M. indica* [18] | Leaf [18] | Hydroal coholic (Soxhlet) [18] | In vivo (Wistar rats, 7 days) [18] | Neuroprotective [18]. |

 

| | | | | | | |
|---|---|---|---|---|---|---|
| Yadav et al., 2020 | Yes | *M. longifolia* [19] | Bark [19] | Aqueous-alcoholic (microwave-assisted) [19] | In vivo (C57BL/6 mice, 21 days) [19] | Anti-melanoma [19]. |
| Neha et al., 2022 | Yes | *M. longifolia* [7] | Leaves [7] | Methanol (Soxhlet) [7] | In vivo (Swiss albino mice) [7] | Antidepressant [7]. |
| Chakraborty et al., 2023 | Yes | *M. longifolia* [8] | Leaves [8] | 70% ethanol [8] | In vitro (MIC, disc diffusion) [8] | Antimicrobial (MDR bacteria) [8]. |
| Khare & Khare, 2023 | Yes | *M. longifolia* [4] | Leaf [4] | Ethanol (Soxhlet) [4] | In vivo (Swiss albino mice, 28 days) [4] | Neuroprotective / memory enhancing [4]. |
| Supplementation of *Madhuca* lon, 2023 | Yes | *M. longifolia* [10] | Seed oil [10] | Commercially obtained [10] | In vivo (Wistar rats, 10 days) [10] | Hepato-/nephroprotective [10]. |
| Yadav et al., 2019 | Yes | *M. longifolia* [3] | Bark [3] | Microwave-assisted aqueous-alcoholic [3] | In vitro (B16F10, A375 cell lines) [3] | Anti-melanoma [3]. |
| Ranjith et al., 2025 | Yes | *M. indica* [11] | Flower [11] | Aqueous /methanol [11] | In vitro (DPPH, molecular docking) [11] | Anti-inflammatory/antioxidant [11]. |
| Nikhade et al., 2025 | Yes | *M. longifolia* [5] | Leaf [5] | Ethanol (Soxhlet) [5] | In vivo (rotenone-induced PD rat model, 28 days) [5] | Neuroprotective (Parkinson's disease) [5]. |
| Singh, 2019 | Yes | *M. longifolia* [20] | Leaf [20] | Aqueous [20] | In vivo (Wistar rats) [20] | Chemopreventive (hepatic cancer) [20]. |
| Pal et al., 2019 | Yes | *M. longifolia* [12] | Flower [12] | Ethanol (Soxhlet) [12] | In vitro (disc diffusion) [12] | Antimicrobial [12]. |
| Periyanayagam et al., 2026 | Yes | *M. longifolia* [21] | Leaf and bark [21] | Ethanol [21] | In vitro (DPPH, $H_2O_2$, BSA denaturation) [21] | Antioxidant / anti-inflammatory [21]. |
| Dhoubhadel et al., 2023 | Yes | *M. longifolia* [2] | Bark [2] | Hexane, DCM, ethyl acetate, methanol, aqueous methanol [2] | In vitro (DPPH, agar well diffusion) [2] | Antioxidant / antibacterial [2]. |
| Nasiruddin et al., 2013 | Yes | *M. indica* [15] | Leaf, bark, seed [15] | 50% ethyl alcohol [15] | In vivo (fish, 24 h exposure) [15] | Toxicological (histopathology) [15]. |
| Udupa et al., 2021 | Yes | *M. longifolia* (syn. *M. indica*) [22] | Seed cakes [22] | Hot and cold acetone, hexane, ethyl acetate [22] | In vitro (well diffusion, cyclic voltammetry) [22] | Antimicrobial/antioxidant [22]. |
| Saif et al., 2025 | Yes | *M. longifolia* [13] | Flowers [13] | 95% ethanol [13] | In vivo (male poultry) [13] | Aphrodisiac [13]. |
| Agrawal et al., 2011 | Yes | *M. longifolia* [23] | Stem-bark [23] | Methanol (Soxhlet) [23] | In vitro (DPPH, ABTS, $H_2O_2$, NO, OH scavenging) [23] | Antioxidant [23]. |
| Khare et al., 2022 | Yes | *M. longifolia* [14] | Leaves [14] | Ethanol (Soxhlet) [14] | In vivo (Swiss albino mice, 14 days) [14] | Acute oral toxicity [14]. |

 

Full texts were retrieved for all 23 studies. The plant parts investigated span leaves (11 studies), bark (7 studies), seeds or seed oil/cakes (4 studies), flowers (3 studies), and stem-bark (1 study), with one comparative toxicology study examining leaf, bark, and seed simultaneously [15]. The dominant species studied was *M. longifolia*, with three studies using the synonym *M. indica* [11, 15, 18]. Ethanol-based extraction (via Soxhlet or maceration) was the most common method, though aqueous, methanol, hydroalcoholic, and sequential solvent extraction approaches were also employed. In vivo studies used rodent models (Wistar rats, Swiss albino mice, C57BL/6 mice), as well as poultry and fish; in vitro studies used cancer cell lines (MCF-7, HT-29, HCT116, B16F10, A375), normal cell lines Fetal Human Colonic (FHC), and microbial cultures.

**Pharmacological Activities by Plant Part**

Table 2 organizes the key quantitative findings according to plant part and pharmacological activity.

**Table 2.** The pharmacological activities of plant parts in different extraction solvents.

| Plant part | Activity | Key quantitative findings | Reference |
|---|---|---|---|
| Leaf | Anticancer (breast, MCF-7) | $IC_{50}$ of ethyl acetate fraction: 14.37 µg/mL; n-butanol: 19.58 µg/mL (cf. tamoxifen 4.59 µg/mL) [17] | Kendre & Wakte, 2022. |
| Leaf | Hepato-/nephro-/gastroprotective | Normalized AST, ALT, ALP, urea, creatinine; comparable to silymarin [6] | Simon et al., 2020. |
| Leaf | Neuroprotective (colchicine model) | GSH increase ($P < 0.001$), NO and AChE decrease ($P < 0.001$) at 100–200 mg/kg [4] | Khare & Khare, 2023. |
| Leaf | Neuroprotective (rotenone PD model) | GSH: 4.91 ± 0.2 µmol/mg (500 mg/kg) vs. 3.79 ± 0.1 (negative); LPO: 1.1 ± 0.21 vs. 2.55 ± 0.4 nmol/g; TNF-α: 90 ± 0.2 vs. 145 ± 0.3 pg/mL ($P < 0.05$ to $P < 0.001$) [5] | Nikhade et al., 2025. |
| Leaf | Neuroprotective (amnesia model) | Significant reduction in glucose and cholesterol; improved escape and transfer latency at 200 and 400 mg/kg [18] | Bala et al., 2025. |
| Leaf | Antidepressant | Significant decrease in immobility (FST, TST) and ptosis at 75–750 mg/kg ($P < 0.01$) [7] | Neha et al., 2022. |
| Leaf | Chemopreventive (hepatic cancer) | Attenuated SOD, catalase, GPx, GSH, G6PD, vitamin C; reduced TNF-α, IL-1β, IL-10, NF-κB [20] | Singh, 2019. |
| Leaf | Antimicrobial (MDR bacteria) | MIC: 1.56 mg/mL (*E. coli*, *K. pneumoniae*); 0.78 mg/mL (P. aeruginosa, S. aureus, MRSA) [8] | Chakraborty et al., 2023. |
| Leaf and bark | Antibacterial | Zone of inhibition: 13.5–15.5 mm (methanol leaf); bark showed higher efficacy overall [16] | S. T. et al., 2021. |
| Leaf and bark | Antioxidant / anti-inflammatory | DPPH scavenging: 71.35% at 250 µg/mL; $H_2O_2$ scavenging: 49.34% at 50 µg/mL; BSA denaturation inhibition: 44.55% at 100 µg/mL [21] | Periyanayagam et al., 2026. |
| Bark | Anticancer (colon, HT-29/HCT116) | IC50 MLE: 3.06 ± 0.93 µg/mL (HT-29), 0.012 ± 0.007 µg/mL (HCT116); synergy with SN-38 (CI <1) [1] | Barycka et al., 2026. |

 

| | | | |
|---|---|---|---|
| Bark | Anti-melanoma (in vitro) | Native bark: 65.15% inhibition; F@AuNp: 85.15% inhibition at 100 µg/mL [3] | Yadav et al., 2019. |
| Bark | Anti-melanoma (in vivo) | F@AuNp at 150 mg/kg: 85.15% inhibition; enhanced WBC; no organ toxicity [19] | Yadav et al., 2020. |
| Bark | Antioxidant | DPPH IC50: 18.86 ± 1.07 µg/mL (methanol extract) [2] | Dhoubhadel et al., 2023. |
| Bark | Antibacterial | Inhibition zones 15–22 mm against S. aureus and *E. coli* [2] | Dhoubhadel et al., 2023. |
| Stem-bark | Antioxidant | DPPH IC50: 20.01 µg/mL; ABTS IC50: 53.82 µg/mL; superior to BHT [23] | Agrawal et al., 2011. |
| Seed | Hepatoprotective | Significant ($P < 0.05$) reduction in SGOT, SGPT, ALP, bilirubin; enhanced SOD, CAT, GSH at 200 and 400 mg/kg [9] | Wardhan & Sharma, 2025. |
| Seed oil | Hepato-/nephroprotective | 1 mL pre-treatment reduced ALP, ALT, AST, urea, uric acid, creatinine ($P < 0.05$) [10] | Supplementation of *Madhuca* lon, 2023. |
| Seed cakes | Antimicrobial / antioxidant | ZI 8.1 mm against S. aureus (cold acetone fraction) [22] | Udupa et al., 2021. |
| Flower | Anti-inflammatory / antioxidant | DPPH scavenging: 65–90% (dose-dependent, 10–50 µg/mL) [11] | Ranjith et al., 2025. |
| Flower | Antimicrobial | Mild to moderate activity; maximum against S. aureus (10.5 mm at 50 µg/mL) [12] | Pal et al., 2019. |
| Flower | Aphrodisiac | Increased sperm concentration, live sperm %, and semen volume in poultry at 1/5th LD50 [13] | Saif et al., 2025. |

Several patterns emerge from these findings. Leaves are the most extensively studied plant part and demonstrate the broadest pharmacological profile, spanning neuroprotective, hepatoprotective, anticancer, antimicrobial, antidepressant, and chemopreventive activities. Bark extracts show particularly potent anticancer effects, with *M. longifolia* bark extract achieving an IC50 as low as 0.012 µg/mL against HCT116 colon cancer cells [1], and native bark ethanolic extract yielding 65.15% anti-melanoma inhibition that was enhanced to 85.15% via flavonoid-loaded gold nanoparticles [3]. Seed and seed oil preparations are primarily associated with hepatoprotective and nephroprotective activities [9, 10], while flowers exhibit moderate antimicrobial, antioxidant, and anti-inflammatory effects [11, 12], along with a unique aphrodisiac activity documented in poultry [13].

**Antioxidant Activity Across Plant Parts**

Antioxidant activity was assessed in multiple studies using DPPH radical scavenging as a common assay, enabling cross-study comparison. The bark methanol extract showed the lowest DPPH IC50 value at 18.86 ± 1.07 µg/mL [2], followed by stem-bark methanol extract at 20.01 µg/mL [23]. The combined leaf and bark ethanolic extract achieved 71.35% DPPH scavenging at 250 µg/mL [21], while the *M. indica* flower extract showed 65–90% scavenging at 10–50 µg/mL [11]. These results suggest that bark-derived preparations may possess stronger radical scavenging capacity on a per-weight basis, potentially attributable to higher concentrations of condensed tannins (980 ± 10.75 mg CE/g) and flavonoids (975 ± 13.31 mg CE/g) in bark methanol extracts [2].

**Anticancer Activity**

Anticancer effects were documented for both leaf and bark extracts, but against different cancer types. Leaf extracts (ethyl acetate fractions) showed IC50 values of 14.37 µg/mL against MCF-7 breast cancer cells [17], while bark extracts demonstrated substantially greater potency against colon cancer

 

cells, with IC50 values of 3.06 µg/mL (HT-29) and 0.012 µg/mL (HCT116) [1]. The bark extract also demonstrated synergistic interaction with SN-38, with combination index values below 1 [1], suggesting clinical potential as an adjunct therapy. Both leaf and bark anticancer activities appear to operate through ROS-mediated apoptosis pathways [1, 17]. In melanoma models, bark-derived flavonoid-loaded gold nanoparticles enhanced anti-melanoma efficacy from 65.15% to 85.15% [3], with the mechanism involving increased caspase-3 activity and nitric oxide release [3].

**Neuroprotective Activity**

Three studies examined neuroprotective effects of leaf extracts using distinct animal models. In a colchicine-induced amnesia model, the ethanolic leaf extract flavonoid fraction at 100–200 mg/kg significantly increased GSH levels ($P < 0.001$) and decreased NO and AChE levels ($P < 0.001$) [4]. In a rotenone-induced Parkinson's disease model, *M. longifolia* leaf extract at 500 mg/kg restored GSH to 4.91 ± 0.2 µmol/mg protein (versus 3.79 ± 0.1 in disease controls), reduced LPO to 1.1 ± 0.21 nmol/g protein (versus 2.55 ± 0.4), and lowered TNF-α to 90 ± 0.2 pg/mL (versus 145 ± 0.3) [5]. The combination of *M. longifolia* extract with voglibose showed the most pronounced neuroprotective effect, with TNF-α reduced to 80 ± 0.2 pg/mL [5]. In an amnesia model using *M. indica*, MLE at 200 and 400 mg/kg significantly improved escape and transfer latency [18]. Across all three studies, the neuroprotective mechanism was consistently attributed to antioxidant enhancement and reduction of oxidative stress markers [4, 5, 18].

**Hepatoprotective and Organ-Protective Activity**

Hepatoprotective activity was demonstrated across seed, seed oil, and leaf preparations. The ethanolic seed extract (200 and 400 mg/kg) significantly reduced Serum Glutamic-pyruvic Transaminase, Serum Glutamic-Oxaloacetic Transaminase, Alkaline Phosphate (SGOT, SGPT, ALP), and bilirubin while enhancing (Superoxide Dismutase, Catalase, Reduce Glutathione) SOD, CAT, and GSH in a CCl4-induced hepatotoxicity model, with the higher dose showing greater efficacy [9]. *Madhuca longifolia* seed oil at 1 mL pre-treatment normalized liver enzyme markers Alanine transaminase, Aspartate transaminase, Alkaline (ALP, ALT, AST) and renal markers (urea, uric acid, creatinine) in a diclofenac-induced toxicity model [10]. The aqueous leaf extract at 500 mg/kg similarly protected liver, kidney, stomach, and intestine against diclofenac-induced damage, performing comparably to silymarin [6]. These findings suggest that the hepatoprotective activity is not restricted to a single plant part, although seed-derived preparations appear to be the most consistently studied for this endpoint.

**Antimicrobial Activity *Escherichia coli* Minimum Inhibitory Concentration**

Antimicrobial properties were documented across leaves, bark, flowers, and seed cakes. The ethanolic leaf extract showed Minimum Inhibitory Concentration (MIC) values of 0.78–1.56 mg/mL against MDR bacterial strains including Methicillin-resistant *Staphylococcus aureus* (MRSA) [8] and demonstrated synergistic effects when combined with amikacin and ceftazidime-avibactam [8]. Bark extracts yielded inhibition zones of 15–22 mm against *S. aureus* and *Escherichia coli* (*E. coli*) [2], while leaf and bark methanol extracts showed zones of 13.5–15.5 mm [16]. Flower ethanol extracts exhibited milder antimicrobial activity, with a maximum zone of inhibition of 10.5 mm against *S. aureus* at 50 µg/mL [12]. Seed cake cold acetone extracts showed modest activity (Zone of Inhibition 8.1 mm against *S. aureus*) [22]. Direct comparison between leaf and bark in a single study indicated that bark extracts demonstrated higher efficacy, which was attributed to a greater concentration of bioactive compounds [16].

**Active Phytochemical Constituents**

The prior artwork had explored the phytocompound consortia of different plant parts as enlisted in Table 3.

Flavonoids, tannins, and phenolic compounds were consistently identified across all plant parts [1, 2, 8, 9, 16, 17, 21]. Bark extracts contained the highest quantified levels of flavonoids (975 mg CE/g)

 

and condensed tannins (980 mg CE/g) [2], which may underlie the potent antioxidant and anticancer activities observed in bark-based studies. Quercetin was specifically identified in multiple leaf and bark studies as a key contributor to antimicrobial [8], neuroprotective [4], and anti-melanoma [19] activities. The seed oil was distinct in its phytochemical profile, dominated by oleic acid (75.83%), which was proposed as the principal agent against oxidative stress [10]. Triterpenes – such as squalene, lupeol, and β-amyrin – were identified primarily in bark hexane extracts and were associated with anti-inflammatory activity [2].

**Table 3.** The key phytocompounds of different plant parts of *Madhuca* sp.

| Plant part | Key phytochemicals | Quantitative content | Associated activity |
|---|---|---|---|
| Leaf | Flavonoids, phenolic compounds | Flavonoids: 14.17 ± 0.56 QE mg/g; phenolics: 299.32 ± 2.73 mg/g [4] | Neuroprotective, antioxidant [4]. |
| Leaf and bark | Phenols, flavonoids, tannins | Phenols: 166.75 ± 14.60 mg GAE/g; flavonoids: 307.93 ± 36.33 mg QE/g; tannins: 23.81 ± 10.00 mg/g [21] | Antioxidant, anti-inflammatory [21]. |
| Bark | Flavonoids, condensed tannins, triterpenes | Flavonoids: 975 ± 13.31 mg CE/g; condensed tannins: 980 ± 10.75 CE/g; phenolics: 196 ± 15.28 mg GAE/g [2] | Antioxidant, antibacterial, anti-inflammatory [2]. |
| Bark | Quercetin, 3,6-dihydroxyflavone | Total phenolics: 35.94 mg/g; flavonoids: 12.15 mg/g [19] | Anti-melanoma [19]. |
| Bark | Squalene, β-amyrin, lupeol, lupeol acetate | Identified by GC-MS in hexane extract [2] | Anti-inflammatory [2]. |
| Stem-bark | Tannins, phenolics, coumarins | Tannins: 17%; total phenolics: 2.15 mg/g [23] | Antioxidant [23]. |
| Seed oil | Oleic acid, n-hexadecanoic acid, β-amyrone | Oleic acid: 75.83%; n-hexadecanoic acid: 3.52%; β-amyrone: 2.54% [10] | Hepatoprotective, anti-oxidative stress [10]. |
| Flower | Flavonoids, tannins, saponins, alkaloids | Qualitative identification [11] | Anti-inflammatory, antioxidant [11]. |
| Leaf | Myricetin, quercetin, β-carotene, oleanolic acid, β-sitosterol | Qualitative identification [5] | Anti-inflammatory, antioxidant [5]. |

## SAFETY AND TOXICITY

The safety assessment of *Madhuca* sp. extract from different parts of the part are enlisted in Table 4.

**Table 4.** Safety Assessment of the extract from different parts of *Madhuca* sp.

| Study | Plant part | Safety/toxicity finding |
|---|---|---|
| Wardhan & Sharma, 2025 | Seed | Safe up to 2000 mg/kg (OECD 423) [9]. |
| Bala et al., 2025 | Leaf (*M. indica*) | No harmful effects at 2000 mg/kg [18]. |
| Khare & Khare, 2023 | Leaf | No harm observed at doses up to 2000 mg/kg [4]. |
| Khare et al., 2022 | Leaf | No mortality or adverse effects at 2500 mg/kg; LD50 >2500 mg/kg [14]. |
| Neha et al., 2022 | Leaf | LD50 of 1000 mg/kg [7]. |
| Barycka et al., 2026 | Bark | Selective toxicity: <20% viability reduction in normal FHC cells at 200 µg/mL [1]. |
| Yadav et al., 2019 | Bark | No toxicity to normal lymphocytes [3]. |
| Yadav et al., 2020 | Bark | No organ toxicity; biocompatible and non-toxic to human lymphocytes [19]. |
| Nasiruddin et al., 2013 | Leaf, bark, seed | Histopathological damage in fish gill, liver, intestine; toxicity ranking: seed > bark > leaf [15]. |

Acute oral toxicity studies in rodents consistently demonstrated a favorable safety profile for *Madhuca* leaf and seed extracts, with no mortality or adverse effects observed at doses ranging from

 

2000 to 2500 mg/kg [4, 9, 14, 18]. One study reported a lower LD50 of 1000 mg/kg for the methanolic leaf extract [7], a discrepancy that may reflect differences in extraction solvent (methanol versus ethanol) or animal strain (Swiss albino mice versus Wistar rats). Bark-derived extracts showed selective cytotoxicity toward cancer cells with minimal effects on normal epithelial cells [1] and lymphocytes [3]. Notably, the only study directly comparing toxicity across plant parts used a fish model and found the order of toxicity to be seed > bark > leaf for gill and intestine, and seed > leaf > bark for liver [15]. This pattern suggests that seeds contain the highest concentrations of bioactive (and potentially toxic) constituents, consistent with the traditional use of *Madhuca* seed in piscicide applications.

**Comparative Efficacy Across Plant Parts**

Only one study (M. Nasiruddin et al., 2013) directly compared the biological effects of different plant parts under identical experimental conditions, finding that seed extracts were most potent (though in this case for toxicity), followed by bark, then leaf [15]. Across the broader evidence base, indirect comparisons can be drawn. For antioxidant activity, bark methanol extracts yielded DPPH IC50 values of approximately 19–20 µg/mL [2, 23], whereas leaf and bark combined ethanolic extracts required 250 µg/mL to achieve 71% scavenging [21], suggesting bark alone may harbor greater antioxidant potency. For anticancer applications, bark extracts showed sub-microgram IC50 values against colon cancer [1], whereas leaf ethyl acetate fractions had IC50 values of approximately 14 µg/mL against breast cancer [17], though these involve different cancer types and are not directly comparable. For antimicrobial activity, the single study comparing leaf and bark concluded that bark exhibited maximum efficacy against both Gram-positive and Gram-negative bacteria, attributed to higher bioactive compound concentrations [16]. Flower extracts generally showed the mildest activity, with lower zones of inhibition [12] and their pharmacological profile more oriented toward antioxidant and anti-inflammatory effects [11].

**MECHANISMS OF ACTION**

Across all plant parts, the pharmacological activities of *Madhuca* converge on a limited number of mechanistic pathways. The dominant mechanism is antioxidant-mediated cytoprotection, documented in hepatoprotective [9, 10], neuroprotective [4, 5], and organ-protective [6] contexts. Seed, leaf, and bark preparations all enhanced endogenous antioxidant enzymes Superoxide Dismutase, Catalase, Glutathione System (SOD, CAT, GSH) and reduced lipid peroxidation [5, 9, 10]. Anti-inflammatory effects, observed in leaf and bark preparations, operate through suppression of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) and NF-κB [5, 11, 20]. Anticancer mechanisms include ROS-mediated apoptosis induction [1, 3, 17], increased caspase-3 activity [3], and inhibition of angiogenesis [19]. The neuroprotective mechanism specifically involves acetylcholinesterase inhibition [4], while antidepressant activity is proposed to involve serotonin reuptake inhibition [7]. Antimicrobial activity is attributed to tannin–protein complexation inhibiting bacterial protein synthesis [16] and flavonoid-mediated disruption of bacterial cell walls [22].

**Synthesis**

The heterogeneity in findings across the 23 studies can be reconciled through several considerations. First, the apparent superiority of bark extracts in antioxidant and anticancer assays is mechanistically consistent with their substantially higher flavonoid and condensed tannin content (975 and 980 mg CE/g, respectively) [2] compared to leaf preparations (14.17 mg QE/g for flavonoids) [4]. The roughly 70-fold difference in flavonoid concentration between bark and leaf may explain why bark achieves sub-microgram IC50 values against cancer cells [1] while leaf fractions require concentrations one to two orders of magnitude higher [17]. Second, the broader pharmacological versatility of leaf extracts – spanning neuroprotection, hepatoprotection, and antidepressant activity – likely reflects a more complex phytochemical composition including myricetin, quercetin, β-carotene, oleanolic acid, and β-sitosterol [5], each with distinct molecular targets. Third, the discrepant LD50 values for leaf extracts (1000 mg/kg in one study [7] versus >2500 mg/kg in another [14]) likely reflect extraction solvent differences: the methanolic extraction used in the former study [7] may concentrate different (and potentially more toxic) alkaloid fractions than ethanol-based protocols [14].

 

The dose-response relationships across studies support a consistent pattern. In hepatoprotective studies, the 400 mg/kg seed extract showed greater efficacy than the 200 mg/kg dose [9], and in neuroprotective studies, the 500 mg/kg leaf extract outperformed the 200 mg/kg dose for nearly all biochemical markers [5]. For antidepressant activity, dose-dependent reductions in immobility were observed at 75, 350, and 750 mg/kg [7]. However, for organ-protective seed oil, the lower 1 mL dose showed greater efficacy than the 2 mL dose [10], suggesting a potential biphasic response or diminishing returns at higher oil volumes. The cancer cell selectivity observed in bark extracts – more toxic to cancer cells than normal epithelium [1] – combined with the absence of toxicity to normal lymphocytes [3] provides an important safety advantage for further development of bark-derived preparations for oncological applications.

## CONCLUSION

The systematic analysis provided insight into the differentiated pharmacological profile across *Madhuca* plant parts. The bark as the most potent source for anticancer and antioxidant applications due to its concentrated flavonoid and tannin content; leaves are the most versatile part with demonstrated neuroprotective, hepatoprotective, and Central Nervous System (CNS)-active properties; seeds and seed oil are effective hepato-nephroprotective agents but with the highest intrinsic toxicity potential, and flowers are moderate sources of antioxidant and anti-inflammatory compounds with additional aphrodisiac properties. All findings derive from preclinical models, and the absence of human clinical data limits the translational relevance of these conclusions.

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