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# THERAPEUTIC VALUE OF GYMNOSPERMS

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**Abstract**

Non-flowering plants, or gymnosperms, are useful for a variety of purposes in the economy since they can be used to make food, oil, lumber, medicines, decorative items, and industrial resources. Used as a staple meal is gymnosperm from species such as Pinus, Cycas, Chilgoza, Ginko, etc. Perfumes and culinary oils are made from the oil derived from gymnosperm seeds. Gymnosperms have extensive medicinal and wood values in addition to these. In addition to being extremely important to humans, gymnosperms offer food and shelter to wildlife. Gymnosperms are valuable economically for a variety of reasons, including oil production, medical use, and aesthetic appeal. Gymnosperms contain a variety of essential phytochemicals, including stilbenes, tannins, glycosides, polyphenols, alkaloids, and flavonoids. It is possible to use phytochemicals in the production of medications. Their application in contemporary medicine is predicated on phytochemicals. The bark, leaves, seeds, and reproductive cones are the sources of the phytochemicals. The plant extract can be prepared using several techniques, including Maceration, Percolation, Soxhlet extraction, and extraction with ultrasound assistance, among others. The Gymnosperm extract has anti-inflammatory, anti-arthritic, anti-bowel, anti-cancer, anti-heart, and anti-stroke properties. Medications made from leaf extract have the potential to increase blood flow.

**Keywords:** Gymnosperms, phytochemicals, Medications, plant extract

## INTRODUCTION

The name 'Gymnosperm' was created by Theophrastus in his Historia Plantarum (350-287 BCE). However, Robert Brown (1827) coined the name to describe a distinct group of plants within the Spermatophyta that yield naked seeds. They are a primitive group of vascular seed plants dating back to the Devonian Paleozoic period. Gymnosperms are woody perennials that are usually evergreen, which are represented by roughly 1000 species that belong to 83 genera and 12 families and are found primarily in temperate parts of the world. There are 161 taxa (154 species, six variations, and one forma) in India, comprising 46 genera and 11 families. There are 76 indigenous taxa and 19 endemics among them. Gymnosperms are one of the most vulnerable plant families, with 40% of species facing extinction, nearly double the most current estimates for all plants. Apart from its ecological importance in conserving the pure temperate continental settings, this ancient group of plants provides people with a variety of commercial items such as lumber, resins, medicine, and foodstuffs. They have participated in

various therapeutic systems, including contemporary medicine, folk medicine, and traditional medicine. Various species studied have been proven to be medicinally effective in diseases such as asthma, cough, sore throat, diarrhea, hypertension, rheumatism, fever, aphrodisiac, ulcer, diuretic, diabetes, kidney stone issues, bronchitis, etc. Although just a few gymnosperms are utilized in TMS, their importance as a medication cannot be overstated. Apart from medicinal benefits, the trees are harvested for a variety of purposes, resulting in an alarming decline in the conservation status of these tree species. These trees appear to be the source of sustainable usage in the majority of natural ecosystems; and have a limited distribution. These drive the need to protect and develop these plants through in-situ and ex-situ conservation efforts, allowing us to fulfill the demand for raw pharmaceuticals. (1, 2)

**ANTIBACTERIAL ACTIVITY OF GYMNOSPERMS**

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| *Ginkgo biloba* | Leaf | Disc-diffusion and broth-dilution assays. | Methanol extract showed the highest activity (zone of inhibition of 15–21 mm) followed by ethanol (14–19 mm), chloroform (15–20 mm), and hexane (14–19 mm) extracts at 250 $\mu$g/mL. A minimum inhibitory concentration (MIC) of 7.8 $\mu$g/mL was found for the methanol extract against *Agrobacterium tumefaciens, Bacillus subtilis, Escherichia coli, Erwinia chrysanthemi, and Xanthomonas phaseoli*[3] |
| *Pinus cembra* | Bark and Needles | Agar diffusion method | Hydromethanolic extracts (4 mg/well) showed antimicrobial effects against *Staphylococcus aureus*, *Sarcina lutea*, *Bacillus cereus*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Candida albicans*[4] |
| *Ephedra gerardiana* | Root and stem | Pour Plate Method | Methanol crude extract *n*-hexane, chloroform, ethyl acetate, and n-butanol, fractions showed antibacterial activities against all tested microbial strains while aqueous fraction showed no activities against *Bacillus subtilis*, *Kleibsiella pneumoniae*, and *Pseudomonas aeruginosa*.[5] |
| *Taxus wallichiana* | Needle | Disk diffusion method, and minimum inhibitory concentrations (MIC) | Hydromethanolic extracts exhibited activities against *S. marcescens* (16.23 ± 0.26 mm), *B. subtilis* (15.71 ± 0.41 mm), *P. chlororaphis* (12.92 ± 0.34 mm) *and P. palleroniana* (15.43 ± 0.37 mm).[6] |

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| *Gnetum africanum* | Leaf and stem | Agar diffusion method | Aqueous and ethanol extract at 50 g/100 mL showed inhibitory effect against the fungal strains (*C. albicans* and *A. niger*) but had no inhibition on the bacterial strains (*S. aureus, S. typhi* and *E. coli*)[7] |
| *Cedrus brevifolia* | Needles, twigs, branches, and bark | Minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) | Antibacterial activity was observed with the methanol extract of branches presenting the strongest activity against *S. aureus* (MIC, 0.097 mg/mL and MBC, 0.195 mg/mL).[8] |
| *Picea abies* | Essential oils extracted from wood residues | Isothermal calorimetry. | The extracts inhibited the growth of *Escherichia coli*. [9] |
| *Larix decidua* | Bark | Microplate dilution method | Hydroalcoholic extract in the concentration range of 2–200 µg/mL showed antimicrobial activity against *Staphylococcus aureus*, *Streptococcus pyogenes*, *Streptococcus pneumoniae*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* , and *Haemophilus influenza*e compared to that of grapefruit seed extract (GSE)[10] |
| *Thuja compacta* | Leaves | Agar well diffusion method | Acetone, chloroform, methanol, and petroleum ether extracts showed significant activity against Bacillus cereus, Bacillus subtilis and Bacillus megaterium. Only Pseudomonas aeruginosa shows activity against chloroform extract. All the organisms are susceptible to Amoxicillin; Ciprofloxacin; Cotrimoxazole; Gentamicin and Tetracycline[11] |
| *Torreya nucifera* | Leaves and | Minimum inhibitory concentrati | The time-kill assay confirmed that Hydro-distilled essential oils (TNEs) had a bactericidal effect on the oral bacteria S. mutans and S. sobrinus, which is |

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| | branches | on (MIC) was measured by a modified Broth Microdilution method Time-kill curve assay | corroborated by the results of the MIC and MBC assays. The MTT assay also revealed that it showed almost no cytotoxicity against human skin cells even at the concentration showing a bactericidal effect.[12] |
| *Encephalartos laurentianus* | Leaves | Disk agar diffusion method | Methanol extract exhibited antifungal activity against *C. albicans* clinical isolates with MIC values that ranged from 32–256 µg/mL.[13] |
| *Pilgerodendron uviferum* | heartwood | Minimum Inhibitory Concentration (MIC) Ethidium Bromide Accumulation Assay | Essential oil, light petroleum ether extract, dichloromethane extract Inhibit efflux in NorA pumps in S. aureus[14] |
| *Nageia wallichiana* | Leaves and twigs | minimum inhibitory concentration (MIC) | Leaf oil was active against Bacillus subtilis and Candida albicans with the MIC value of 50 µg/mL with Streptomycin, tetracycline and nystatin were used as positive controls [15] |
| *Araucaria araucana* | Wood | Agar-well diffusion | Lignans (secoisolariciresinol, pinoresinol, eudesmin, lariciresinol, and lariciresinol-4-methyl ether) were isolated from an MeOH extract. secoisolariciresinol exhibited a significant antifungal activity on fungi of white rooting and wood staining and this compound completely inhibited the mycelial growth of T. Versicolor and C. pilifera at 300 and 400µg per disc, respectively, whereas pinoresinol showed a moderate inhibitory activity. On the other hand, the MeOH extract had the highest activity against rooting and staining and pathogenic fungi as well as T. versicolor, Fusarium and Trichophyton mentagrophytes, inhibiting completely the growth at 400µg per disc.[16] |

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| *Taxodium ascendens* | Green fruit | MIC | Diterpenes from Taxodium ascendens such as demethylcryptojaponol, 6-hydroxysalvinolone, hydroxyferruginol, and hinokiol demonstrated potent activity against clinical isolates of methicillin-resistant Staphylococcus aureus (MRSA).[17] |
| *Agathis dammara* | Leaves | Disc diffusion method and micro-well dilution assay | Essential oil had significant antibacterial activities with inhibition zones against Staphylococcus aureus and Pseudomonas aeruginosa were 23.7 and 23 mm, respectively, which demonstrated that the inhibition effects were greater than positive control (10 µg/disc streptomycin)<br>The lowest MIC value was found against S. aureus (1.25 mg/mL) and Bacillus subtilis (1.25 mg/mL).[18] |

**ANTI-INFLAMMATORY ACTION OF GYMNOSPERMS**

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| *Torreya nucifera* | Seeds | Lipopolysaccharide-activated RAW264.7 cells | Ethyl acetate fraction (Tn-EE-BF) inhibits NO and $PGE_2$ production and also blocks mRNA levels of inducible NO synthase (iNOS), (TNF)-α, and cyclooxygenase (COX)-2 in a dose-dependent manner. Tn-EE-BF reduces nuclear levels of the transcriptional factors NF-κB (p65) and AP-1 (c-Jun and FRA-1. It also inhibits phosphorylation levels of Src and Syk in the NF-κB pathway, as well as, IRAK1 at the protein level, part of the AP-1 pathway. By kinase assay, we confirmed that Src, Syk, and IRAK1 are suppressed directly. HPLC analysis indicates that arctigenin, amentoflavone, and quercetin may be active components with anti-inflammatory activities.[19] |
| *Amentotaxus yunnanensis* | Leaves | LPS-activated RAW264.7 cells | Amenyunnaosides A-C inhibited NO production in LPS-activated RAW264.7 cells with their $IC_{50}$ values ranging from 11.05 to 44.07 µM, compared to that of the positive control compound, dexamethasone, $IC_{50}$ value of 16.93 µM. |

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| | | | Additionally, amenyunnaoside A dose-dependently reduced the production of IL-6 and COX-2 but did not affect that of TNF-α at concentrations of 0.8, 4, and 20 μM.[20] |
| *Taxus baccata* | Bark | Carrageenan-induced paw edema method in the rat. | 95% ethanol extract exhibits potent anti-inflammatory activity at 200mg/kg four hours after administration in comparison with ether extract, as well as reference standard, Aspirin. The percentage inhibition of edema was 44.44% at a dose of 200 mg/kg of 95% ethanol extract which is comparable to that of Aspirin[21] |
| *Cupressus torulosa* | Needles | Egg albumin denaturation assay while carrageenan-induced paw edema and formalin-induced paw edema models | 25% aqueous methanol (AM) demonstrated promising in vitro anti-inflammatory activity ($IC_{50}$ 160.01 μg/mL) compared to standard diclofenac sodium ($IC_{50}$ 73.94 μg/mL) in egg albumin denaturation assay. In carrageenan-induced paw edema and formalin-induced paw edema tests the extract showed significant anti-inflammatory activity (57.28% and 51.04% inhibition of paw edema, respectively) at the dose of 400 mg/kg p.o. after 4 h in comparison to the standard diclofenac sodium which displayed 61.39% and 52.90% inhibition, respectively, at the dose of 10 mg/kg p.o. after 4 h in these models. Two compounds namely monotropein (iridoid glycoside), (±)12-HETE (eicosanoid), and fraxin (coumarin glycoside) were reported to have anti-inflammatory effects.[22] |
| *Chamaecyparis obtusa* | Leaf | NF-κB-induced inflammation in WI38 fibroblast cells | Western blot analysis revealed the essential oil inhibition of inducible nitric oxide synthase, activation of cyclooxygenase-2, and the degradation of cytosolic p65 and inhibitor of NF-κB-α in the LPS-stimulated group. Additionally, confocal imaging of |

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| | | | nuclei revealed the translocation of phosphorylated p65, which was recovered in the cytosol in the phytoncide essential oil pre-treated group. Histopathological observation revealed that the alveolar capacity was enhanced in the essential oil olfactory administered rat group, compared with that in the normal rat group.[23] |
| *Thuja occidentalis* | Fresh, young, non woody branches with leaves | Cell viability assays on Caco-2 colon cells and ultrastructural analysis of the intestinal mucosa, measurement of reduced glutathione, lipid peroxidation, and gene expression of the inflammation markers in the intestine after oral administration to an experimental mouse model of colon inflammation (colitis) developed by intrarectal administration of 2,4,6- trinitro benzene sulfonic acid (TNBS). | Administration of 25 or 50 mg *T. occidentalis* mother tincture (MT) by gavage for 7 days succeeded in inhibiting the inflammatory process induced by TNBS in the intestine, most probably because of its rich contents of flavonoids and phenolic compounds.[24] |
| *Callitris columellaris* | Leaf | Rat paw edema | Essential Oil causes a significant reduction in inflammation i.e., 60% (1000 µg/kg p.o.) compared to standard anti-inflammatory drug indomethacin i.e., 40% (25 mg/kg)[25] |
| *Araucaria bidwillii* | Leaf | Hot Plate Method | The leaf hydroalcoholic extract at 300 and 200 mg/kg showed a significant reduction in acetic acid-induced writhings in mice |

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| | | Acetic Acid-Induced Writhing Test. Carrageenan Induced Rat Paw Oedema. Serotonin Induced Rat Paw Oedema. | with a maximum effect of 65.1% reduction at 300 mg/kg dose. In the hot plate method, the percentage of pain inhibition was found to be 81.69% and 66.1% with both the tested doses of the leaf extract respectively. The effect produced by the alcoholic extract at the highest dose was comparable to that of acetylsalicylic acid at 100 mg/kg (91.52%). The alcoholic extracts also showed significant inhibition in carrageenan (18.61%, 32.12%, and 45.64%) and serotonin (32.81%, 38.68%, and 40.75%) induced hind paw edema in rats at 100, 200, and 300 mg/kg of the ABH extract respectively. The anti-inflammatory effects showed by the extract were comparable to that of standard indomethacin 5 mg/kg (68.51% and 63.28%)[26] |
| *Podocarpus macrophyllus* | Twigs and leaves | LPS-Induced HT-29 and RAW 264.7 Cells | nagilactone B and 16-hydroxy-4β-carboxy-*O*-β-D-glucopyranosyl-19-nor-totarol diterpenoids from *P. macrophyllus* exhibited a potent anti-inflammatory effect against NO production on RAW 264.7 cells. Western blot analysis revealed that nagilactone B significantly decreased the expression of LPS-stimulated protein, inducible nitric oxide synthase (iNOS), cyclooxygenase (COX)-2, and phosphorylated extracellular regulated kinase (pERK)1/2. It also downregulated tumor necrosis factor (TNF)-α, interleukin (IL)-6, and IL-8 levels in LPS-induced macrophages and colonic epithelial cells.[27] |
| *Pinus roxburghii* | Leaves | Acetic acid-induced writhing and tail immersion tests in Swiss albino mice | The alcoholic extract of *Pinus roxburghii* Sarg. at doses 100, 300, and 500 mg/kg showed significant inhibition of |

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| | | Carrageenan induced paw edema and cotton pellet granuloma in Wistar albino rats. | paw edema at the third hour as compared to indomethacin<br>The alcoholic bark extract exhibited a significant and dose-related inhibition of the dried weight of the cotton pellet granuloma comparable to Diclofenac sodium.<br>The dose of 500 mg/kg significantly reduced the number of abdominal constrictions induced in mice by a solution of acetic acid 1%.<br>After 90 minutes the extract in doses of 300 mg/kg and 500 mg/kg body weight showed a significant elongation of reaction time in the Tail Immersion Test in Rats.[28] |

**ANTIDIABETIC EFFECTS OF GYMNOSPERMS**

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| *Cycas edentata* | Leaf | Alloxan-induced diabetic ICR mice | At doses between 250 and 1000 mg/kg body weight, the aqueous extract showed an antihyperglycemic effect and significantly lowered cholesterol comparable to Glimepiride.[29] |
| *Ginkgo biloba* | Leaf | Randomized, placebo-controlled, double-blinded, and multicenter clinical trial | The extract significantly decreased blood HbA1c (7.7%±1.2% vs baseline 8.6%±1.6%, $P$<0.001), fasting serum glucose (154.7±36.1 mg/dL vs baseline 194.4±66.1 mg/dL) and insulin (13.4±7.8 µU/mL vs baseline 18.5±8.9 µU/mL, BMI (31.6±5.1 kg/m$^2$ vs baseline 34.0±6.0 kg/m$^2$), waist WC (102.6±10.5 cm vs baseline 106.0±10.9 cm), and VAI (158.9±67.2 vs baseline 192.0±86.2).[30] |
| *Encephalartos ferox* | Leaves | Haemoglobin glycation<br>α-Glucosidase inhibitory activity<br>Pancreatic lipase inhibitory activity | The crude extract exhibited the antidiabetic potential as it significantly inhibited α-glucosidase and pancreatic lipase in a dose dependent fashion. The extract also effectively reduced intestinal glucose absorption. The extract showed antioxidant activity by efficiently scavenging ABTS and DPPH radicals with $IC_{50}$ values of 68.3 µg/ml and 308 µg/ml, respectively.[31] |

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| *Ephedra foeminea* | Aerial parts | Streptozotocin-Induced Diabetic Rats | In comparison to metformin (100 mg/Kg), induced diabetic rats treated with *Ephedra foeminea* aqueous extract showed significant improvement in blood glucose levels, lipid profile, liver, and kidney functions. Interleukin 1 and glutathione peroxidase levels in the spleen, pancreas, kidney, and liver of induced diabetic rats treated with extract were significantly lower than in untreated diabetic rats.[32] |
| *Cedrus deodara* | Stem bark | Streptozotocin induced diabetes in mice | Ethanolic extract at dose levels of 250 mg/kg and 500 mg/kg exhibited significant antihyperglycemic activity and also lowers the biochemical parameters like SGPT, SGOT, cholesterol and triglycerides. almost near to the effect of 10 mg/kg glibenclamide.[33] |
| *Pinus halepensis* | Bark | Enzymatic inhibition tests (α-amylase and α-glucosidase) | The anti-oxidation activity tests revealed a significant reducing power towards the radicals tested. It also inhibited the enzymes involved in diabetes (α-amylase and α-glucosidase) at very low concentrations comparable to Acarbose. These effects were verified in the in vivo approach, in particular by using the starch tolerance test.[34] |
| *Picea glauca* | Needle, Bark, and Cone | In vitro paradigms of diabetic neuropathy (glucotoxicity and glucose deprivation) in PC12 cells. | Fractions were well-tolerated by PC12 neuronal precursors under normoglucose conditions. $LD_{50}$ concentrations of needle extracts exceeded 100 µg/mL, whereas the $LD_{50}$ of bark and cone extracts was 40 and 36.4 µg/mL respectively. Needle extracts protected PC12 cells from both glucotoxicity and glucose deprivation. Bark extracts had negligible activity. Cone extracts further impaired PC12 cell glucose tolerance.[35] |
| *Abies pindrow* | Aerial Parts | Starch iodine test via α-amylase enzyme inhibition | The methanol extract showed huge antidiabetic action whereas the chloroform extract exhibited a mild profile of antidiabetic potential[36] |
| *Araucaria columnaris* | Leaf | Alloxan induced diabetes | The total phenolic content of benzene, ethyl acetate, methanolic, and aqueous extract were 5.18±0.91, 8.97±0.17, 63.22±0.48 and 38.24±0.63 GAE mg/g, respectively. The $IC_{50}$ value of the DPPH |

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| | | | scavenging potential for benzene and ethyl acetate was found to be more than 250µg/mL whereas for methanol and aqueous extracts was found to be 136.6 and 200.2 µg/mL respectively. The aqueous extract was able to lower the blood glucose more in comparison to the methanolic extract comparable to glibenclamide.[37] |
| *Cupressus sempervirens* | Fruits and Seeds | α-amylase digestion enzyme. | The fruits and seeds contained total free phenolic content of 1.96 and 2.25 mg/g GAE, respectively. The saponin content determined with vanillin reagent shows a good yield of 119.85 and 131.46 mg/g DE in ethyl acetate and butanolic extracts, respectively. In addition, phenolic and saponins extracts were found to inhibit the enzymatic activity of α-amylase under in vitro starch digestion bioassay and the values of the $IC_{50}$ constants have been determined for both seeds and cones extracts. The values ranged from 0.49 to 1.12 mg/ml.[38] |
| *Thuja occidentalis* | Aerial parts | Alloxan monohydrate-induced diabetic model in rats | The hydroalcoholic extract at the dose of 100 mg/kg showed decreased levels of serum glucose, HOMA-IR, total cholesterol, triglycerides, low-density lipid cholesterol, very low-density lipid, alanine amino transaminase, aspartate amino transaminase, lactate dehydrogenase, alkaline phosphatase, acid phosphatase, albumin, creatinine, urea and uric acid and increased levels of serum insulin, HOMA-β, high-density lipid cholesterol, total protein, and impairment in pancreatic β-cell functioning as compared to Glibenclamide (0.5 mg/kg, i.p.).[39] |
| *Chamaecyparis obtusa formosana* | Leaf | Rats with hyperglycemia induced by high-fat diets and streptozotocin | Hot water extracts of *C. obtusa* var. *formosana* leaves showed improved glucose metabolism in oral glucose tolerance and postprandial blood glucose tests. A decrease in HOMA-IR, leptin, and adiponectin levels of the HCO group revealed relieved insulin and leptin resistance. Obesity and accumulation of visceral fats induced by STZ and HFD could be mitigated in extract-treated groups. |

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| | | | These anti-diabetic effects might be attributed to inhibition of intestinal digested enzymes and protein tyrosine phosphatases (PTPases).[40] |
| *Juniperus oxycedrus oxycedrus* | Berries | Streptozotocin-induced diabetic rats | Through in vivo bioactivity-guided fractionation processes, shikimic acid, 4-O-β-D-glucopyranosyl ferulic acid, and oleuropeic acid-8-O-β-d-glucopyranoside were isolated from the n-butanol sub extract of Water extract by silica gel and reverse phase column chromatography as the main active ingredient of the active subfraction. After 8 days of administration of the major compound shikimic acid, blood glucose levels (24%), malondialdehyde levels in kidney tissues (63–64%), and liver enzymes (AST, ALT, ALP) of diabetic rats were decreased.[41] |
| *Cephalotaxus sinensis* | Leaf | STZ-induced diabetic rats | The extract showed significantly decreased fasting blood glucose and increased serum insulin level compared with the untreated diabetic control. Histopathology analysis showed that the pancreas of diabetic rats treated with the extract was more intact than that of untreated ones. The SOD activities in STZ-induced diabetic rats treated with the extract were significantly higher than that in untreated diabetic ones. At the same time, the corresponding MDA levels were much lower in the extract-treated diabetic animals.[42] |

**ANTITUMOR EFFECTS OF GYMNOSPERMS**

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| *Torreya grandis* | Aril | H22 mice models of liver cancer | The n-butanol fraction showed antitumor activity without obvious liver damage through potentiating immunologic function and antioxidant activity of tumor-bearing mice comparable to cyclophosphamide [43] |
| *Taxus cuspidata* | Needles and twigs | MTT assay or ATP assay. H & E, PI, TUNEL staining, as | The extract reached inhibition rates of 70-90% in different human cancer cell lines (HL-60, BGC-823, KB, Bel7402, and HeLa) but only 5-7% in normal mouse T/B lymphocytes, demonstrating the broad-spectrum anticancer |

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| | | well as Annexin V/PI assay. Flow cytometry. | activity and low toxicity to normal cells of TC extract in vitro. It inhibited cancer cell growth by inducing apoptosis and G2/M cell cycle arrest. extract and 5-FU, combined as a cocktail, synergistically inhibited the growth of cancer cells in vitro, with Combination Index values (CI) ranging from 0.90 to 0.26 at different effect levels from $IC_{50}$ to $IC_{90}$ in MCF-7 cells, CI ranging from 0.93 to 0.13 for $IC_{40}$ to $IC_{90}$ in PC-3M-1E8 cells, and CI < 1 in A549 cells. also extract did not affect the pharmacokinetics of 5-FU in rats.[44] |
| *Taxus yunnanensis* | Barks and leaves | A549 Xenograft Mice MTT Assay Western Blotting Flow Cytometry Analysis with Annexin V/PI Staining | *In vivo*, A549 growth is significantly inhibited by 86.1 ± 12.94% at 600 mg/kg of paclitaxel-containing extract (HDS-1) and 65.7 ± 38.71% at 200 mg/kg. HDS-1-derived flavonoids (HDS-2) and lignoids (HDS-3) significantly reduce the efflux ratio of paclitaxel to 2.33 and 3.70, respectively, in Caco-2 permeability experiment and reduce paclitaxel reflux in MDCK-MDR1 experiment. Furthermore, HDS-2 and HDS-3 potentiated paclitaxel-induced cytotoxicity by 19.1–22.45% and 10.52–18.03%, respectively, inhibited the expression of cyclinB1, Bcl-2, and pMCL-1, and increased the percentage of necrosis cell in the condition of paclitaxel exposure.[45] |
| *Calocedrus formosana* | Leaves | Cell viability assay Annexin V-FITC binding assay Western blot analysis Reactive oxygen species (ROS) assay | n-hexane fraction of methanolic extract exhibited the highest cytotoxicity potential against two non-small-cell lung cancer (NSCLC) cell lines, namely A549 and CL1-5. Yatein, isolated from the n-hexane fraction, exhibited the highest cytotoxicity in the A549 and CL1-5 cells. Flow cytometry results revealed that yatein induced apoptosis in the cell lines. Furthermore, expression of regulatory proteins related to apoptosis, such as caspase 3, caspase 8, caspase 9, and poly (ADP-ribose) |

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| | | | polymerase (PARP), increased in the A549 and CL1-5 cells after yatein treatment.[46] |
| *Calocedrus decurrens* | Heartwood | MTT assay | The hexane extract and libocedroquinone displayed excellent cytotoxic effects against the human lung adenocarcinoma (A549) cell line. Moreover, libocedroquinone exhibited less toxicity with normal lung fibroblast cell line WI-38.[47] |
| *Juniperus procera* | Leaves | Flow-Cytometry | Methanolic extract suppresses cancer cells in the colon ($HCT_{116}$), liver (HepG2), breast (MCF-7), and erythroid (JK-1) cell lines. Out of the 12 bioactive compounds reported by GC/MS analysis, the active ingredient 2-imino-6-nitro-2*H*-1-benzopyran-3-carbothiamide proved to be the best-docked chemical with the chosen proteins impacted by DNA conformational changes, cell membrane integrity, and proliferation in molecular docking studies. It was also found that the plant extract induced apoptosis and inhibited cell growth in the $HCT_{116}$ cell line.[48] |
| *Juniperus communis* | Fruits | Cell viability assay. Cell cycle analysis TUNEL assay Immunoblotting analysis | *J. communis* extract (JCo extract) inhibited the growth of human HCC cells by inducing cell cycle arrest at the $G_0/G_1$ phase, extensive apoptosis, and suppressing metastatic protein expressions in HCC cells. Moreover, the combinational treatment of JCo and VP-16 was found to enhance the anticancer effect. In *in vivo* study, JCo extract significantly suppressed HCC tumor growth and extended the lifespan with no or low systemic and pathological toxicity. The extract significantly up-regulated the expression of pro-apoptotic proteins and tumor suppressor p53, suppressed VEGF/VEGFR autocrine signaling, down-regulated cell cycles regulatory proteins and MMP2/MMP9 proteins.[49] |

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| *Cupressus sempervirens* | Leaf | Trypan blue assay. Mean survival days (MST) | The essential oil was able to reduce the DPPH reaching 50% reduction with $IC_{50}$ value = 290.09 7g $mL^{-1}$. It also exerted the highest cytotoxic activity with an $LC_{50}$ of 333.79 µg $mL^{-1}$ against NB4 followed by HL-60 and EACC cell lines (LC50 of 365.41, and 372.43 µg $mL^{-1}$, respectively). Regarding the in vivo anticancer study, pre-initiation treatment with the essential oil was more effective than initiation and post-initiation treatments respectively on the tumor (EACC) transplanted female mice (increased lifespan (%), decreased total EACC number and increased dead cells). In the toxicity study, serum urea, transaminases, and lactate dehydrogenase were increased.[50] |
| *Chamaecyparis lawsoniana* | Leaf | MTT assay | The leaf essential oil showed activity against human breast (MCF-7), colon (HCT-116), lung (A-549), and hepatocellular (HepG-2) carcinoma cells, with significant selectivity indices. It also showed weak antioxidant activity according to the DPPH, ABTS, and FRAP assays. In silico docking of these constituents against the epidermal growth factor receptor (EGFR), the myeloid cell leukemia-1 (Mcl-1) and caspase-8 using Molecular Operating Environment (MOE) software demonstrated good binding affinities of the components with the active site of these targets.[51] |

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| *Chamaecyparis obtusa* | Leaf | MTT assay. Immunoblotting Wound healing assay and trans well migration assay IncuCyte Annexin V Red staining | EtOH extracts at the dose of 100 mg/kg inhibited the tyrosine phosphorylation of pY-STAT3 in MDA-MB-231 breast cancer cells at a concentration of 25 and 50 µg/mL. It also inhibited not only endogenous pY-STAT3 levels but also IL-6-induced STAT3 breast cancer cells. The metastatic potential is inhibited by downregulating the expression of N-cadherin, fibronectin, TWIST, MMP2, and MMP9 in MDA-MB-231 breast cancer cells. It also induced apoptotic cell death by increasing cleaved caspase-3 and decreasing anti-apoptotic proteins Bcl-2 and Bcl-xL.[52] |
| | | MTT assay | The methanol extract of CO leaves, at a concentration of 1.25 µg/mL, exhibited anti-proliferative activity against HCT116 cells, while displaying no cytotoxicity against Chang liver cells. Comparative global metabolite profiling was performed using gas chromatography-mass spectrometry coupled with multivariate statistical analysis, and it was revealed that anthricin was the major compound contributing to the anti-proliferative activity. The activation of c-Jun *N*-terminal kinases played a key role in the apoptotic effect.[53] |
| *Cunninghamia lanceolata var. konishii* | Heartwood | Cell viability assay | The oil possessed cytotoxic activity against human lung, liver, and oral cancer cells. The observed activity was probably due to cedrol.[54] |
| *Cedrus deodara* | Pine needles | MTT assays | The total flavonoids from the pine needles of *Cedrus deodara* (TFPNCD) inhibited the growth of HepG2 cells in a dose-dependent manner, with $IC_{50}$ values of 114.12 µg/mL. It was able to increase the population of HepG2 cells in the $G_0$ /$G_1$ phase and increase the percentage of apoptotic HepG2 cells.[55] |
| *Cedrus libani* | Wood | Cell survival assay | 2-himachalen7-ol (7-HC) isolated from the hexane extracted oil demonstrated potent cytotoxic activity against the brain (SF-268, |

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| | | | $IC_{50}$ 8.1µg/mL) and colon (HT-29, $IC_{50}$ 10.1µg/mL; Caco-2, $IC_{50}$ 9.9µg/mL) with ovarian (SkOV-3, $IC_{50}$>50µg/mL) cells being the most resistant. However, while HT-29 displayed resistance to Cisplatin, 7-HC was 8–10 folds more potent. Co-treatment with 7-HC and Cisplatin showed a synergistic anti-proliferative effect 7-HC also exhibited a significant anti-inflammatory effect in formalin-induced paw edema in rats. Western blot analysis revealed that 7-HC displayed dose-dependent inhibition of LPS-induced COX-2 protein expression in isolated rat monocytes.[56] |
| *Gnetum gnemon* | Seed | Human and murine tumor models in vitro and in a colon-26 tumor-bearing mouse model in vivo | Seed extract (MSE) and its active ingredient gnetin C (GC), at clinically achievable concentrations significantly inhibited the proliferation of pancreatic, prostate, breast, and colon cancer cell types without affecting normal cells. Interestingly, GC exerts enhanced antitumor activity than that of tRV. It also significantly induced apoptosis in all the cancer cells, indicating that MSE and GC inhibit tumor cell growth by inducing apoptosis. Oral administration of MSE at 50 and 100 mg/kg per day significantly inhibited tumor growth, intra-tumoral angiogenesis, and liver metastases in BALB/c mice bearing colon-26 tumors.[57] |
| | | MTT assay | Seed extract collected using the ion exchange DEAE matrix showed cytotoxic activity against cervical cancer (HeLa) and breast cancer (4T1) cell lines. The $IC_{50}$ value was found to be 361,1 µg/mL and 939,723 µg/mL against 4T1 and HeLa cells, respectively.[58] |
| *Ginkgo biloba* | Fresh male flowers | MTT assay | Amentoflavone-7″-*O*-β-d-glucopyranoside, amentoflavone, bilobetin, isoginkgetin, sciadopitysin were isolated from *Ginkgo*. Among them, Bilobetin and isoginkgetin exhibited anti-proliferative activities on cancer |

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| | | | lines. Their effects were found to be cell-specific and in a dose and time-dependent manner for the most sensitive HeLa cells. They were capable of arresting the G2/M phase of the cell cycle, inducing the apoptosis of HeLa cells dose-dependently, and activating the proapoptotic protein Bax and the executor caspase-3. Bilobetin could also inhibit the antiapoptotic protein Bcl-2.[59] |
| | Fruit | LLC solid tumor model in C57BL/6J mice. | *Ginkgo biloba* exocarp extracts (GBEE) at a dose of 50–200 mg/kg inhibited the growth of LLC transplanted tumors with a dose-effect relationship. It inhibited the proliferation of LLC cells in vitro with the $IC_{50}$ value of 162.43 µg/mL, while it had no significant inhibitory effects on the primary cultured mouse lung cells. the apoptosis rate was increased and the MTP was decreased. The ratio of Bax/Bcl-2 was increased in the cells. Meanwhile, it also promoted the translocation of Bax/Bcl-2 in the mitochondrial membrane and the release of Cyt C from mitochondria to cytosol. In addition, it up-regulated the cleaved-Caspase-3 protein expression. The mRNA levels of Fas and the protein levels of Fas, FasL, and p-p38 in the cells were both increased. The levels of p-ERK1/2 and p-JNK1/2 protein was down-regulated but the p38, ERK1/2, and JNK1/2 were not significantly changed.[60] |
| *Ephedra foeminea* | Scale minute leaves and stem | U2OS Doubling Time MTT Cell Viability Assay. Scratch Wound | Ethyl acetate, ethanol, and water crude extracts significantly reduce human osteosarcoma U2OS percentage viability in a dose- and time-dependent manner, with varying potencies. The $IC_{50}$ was observed in the water extract after 48 h incubation (30:761 ± 1:4 µg/mL) followed by the ethyl acetate extract after 72 h incubation (80:35 ± 1:233 µg/mL) and finally the ethanol extract after 48 h incubation (97:499 ± 1:188 |

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| | | Healing Assay. Reverse Transcription Polymerase Chain Reaction | µg/mL). The ethanol extract significantly reduced U2OS percentage wound closure. Also, both ethanol and water extract considerably reduced the steady-state mRNA expression of beta-catenin, promoting both cell proliferation and migration in osteosarcoma by regulating target genes. It also showed no hemolytic activity.[61] |

**ANTIOXIDANT ACTIVITY OF GYMNOSPERMS**

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| 1. Abies pindrow | Leaves | Total phenolics<br>Total flavonoids<br>DPPH radical scavenging assay<br>ABTS radical scavenging assay<br>Superoxide radical scavenging assay<br>Ferric reducing antioxidant power (FRAP)<br>Metal ion chelating activity | The total phenolic, flavonoid and flavonol content of acetone extract was found to be the highest among the tested extracts<br>Methanol extract demonstrated highest activity ($IC_{50}$ 0.163±0.006 mg/ml) as compared to acetone extract ($IC_{50}$ 0.194±0.013 mg/ml) and dichloromethane extract ($IC_{50}$ 3.41±0.331 mg/ml). However, these activities were less than that of standard trolox.<br>The acetone extract was most active in scavenging superoxide radicals with 68.383±2.529 % inhibition, while dichloromethane and methanol extracts showed 51.794±5.183 % and 43.729±0.417 % inhibition respectively at 0.5 mg/ml.<br>All the extracts exhibited chelating activity by interfering ferrous-ferrozine complex in a dose-dependent manner. Among the extracts, methanol extract was the most potent ($IC_{50}$ 0.183±0.008 mg/ml). [62] |
| 2. Cycas beddomei | Male cone | Total Phenolic Content (TPC), Total Flavonoid Content (TFC), Total Flavonols (TF), Total Proanthocyanidins | Aqueous extract reported Total Phenolic Content (TPC, Gallic Acid Equivalent) 135.69±1.53 mg/g; Total Flavonoid Content (TFC 311.39±6.09 mg/g, Quercetin Equivalent); Total Flavanols 145.58±9.75 mg /g (TF, Catechin Equivalent); Total |

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| | | (TPA), DPPH assay, TAC and ABTS assay. | Proanthocyanidines 48.66±1.80 mg/g (TPA, Catechin Equivalent)<br>The lowest DPPH activity was exerted at 25µg/ml concentration (13.00±1.00) and the highest activity was exerted at 250µg/ml (86.00±2.00). The TAC also increased with an increase in the extract concentration. The lowest TAC was observed at 25µg/ml concentration (12.00±1.00) and the highest TAC was observed at 250µg/ml (81.67±1.53). The lowest ABTS activity was exerted at 25µg/ml concentration (16.67±0.58) and the highest activity was exerted at 250µg/ml (42.00±2.65). The lowest DPPH activity has exerted at 25µg/ml concentration (21.00±1.00) and the highest activity was exerted at 250µg/ml (98.67±0.58). The lowest TAC was observed at 25µg/ml concentration (16.67±0.58) and the highest TAC was observed at 250µg/ml (92.67±0.58)[63] |
| 3. *Ginkgo biloba* | Leaves | DPPH<br>Molybdenum-reducing antioxidant power<br>The total polyphenols and flavonoids | The best activity was determined by the free radical scavenging activity (DPPH) (1.545 mg Trolox equivalent antioxidant capacity (TEAC)/g fresh matter (FM)) as well as the molybdenum-reducing antioxidant power (35.485 mg TEAC/g FM) methods. The highest content of total polyphenols (2.803 mg gallic acid equivalent (GAE)/g FM) and flavonoids (4.649 µg quercetin equivalent (QE)/g FM) was also detected.[64] |
| 4. *Gnetum gnemon* | Leaf, bark, twig, and seeds | Total phenolic content<br>DPPH and FRAP assays | Bark from hot water extract showed the highest total phenolic at 10.71 ± 0.01 mg GAE/ FDW, while the lowest was chloroform extract of seed at 2.15 ± 0.01 mg GAE/ FDW. The DPPH results showed that all plant extracts demonstrated weak free radical scavenging activity tested at the final concentration of 300 µg/ml. In contrast, the |

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| | | | methanolic twig extract showed strong reducing power activity (FRAP) at 83.55 ± 1.05%, while the hot water seed extract showed the least activity at 41.86 ± 4.22% tested at the final concentration of 300 µg/ml.[65] |
| 5. *Ephedra alata* | Female Cones | DPPH free-radical scavenging test<br>Hemolysis test<br>Reducing power test<br>Determination of phenolic and flavonoid contents | the methanolic extract has the best content of polyphenols (158.34±2.71mg GAE/g Extract), and the best values of flavonoids (88.50±1.12mg QE/g Extract). The results of the test scavenging the free-radical DPPH show the tannins extract had the best scavenging activity capacity than the other extracts ($IC_{50}$: 14.94±1.34µg/mL). However, in the hemolysis test, all the extracts were in proximity except for the aqueous extract that was shown protected by the erythrocytes (50±0.5% of hemolysis percentage). Finally, in the reducing power assay, its results showed that the tannins extract has the best-reducing power of 27.16±0.25µg/mL in Abs700= 0.5 compared to other extracts.[66] |
| 6. *Cedrus atlantica* | Wood | Total condensed tannins<br>Total polyphenolic content<br>Total antioxidant capacity by phospho molybdenum method<br>Ferric-reducing antioxidant power | Chemical characterization identified Himachalene and α-atlantone isomers (14.51 % - 4.07 %), Calacorene (3.52 %) and ar-Turmerone 3.35 %, as the major components, the total polyphenolic content and condensed tannins contents were 57.15 ± 0.15 mg equivalent of gallic acid /g tar and 4.41 ± 0.05 mg equivalent of catechin /g tar respectively. The extract also showed remarkable Ferric-reducing antioxidant power with an effective concentration equal to 50 ± 0.075 mg /mL ± 0,00028 and total antioxidant capacity equal to 262.75 mg equivalents of ascorbic acid /g tar ± 14,43.[67] |
| 7. *Pinus densiflora* | Barks | DPPH method. | hot water extract exhibited the lowest ROS production. The pattern of HPLC analysis of |

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| | | ROS inhibition activity in a cellular system using MC3T3 E-1 cells | each extract indicated that the hot water extract contained the highest proanthocyanidin level.[68] |
| 8. *Picea smithiana* | Leaf and Bark | DPPH radical scavenging method, $Fe^{2+}$ ion chelating method, FRAP assay, and Potassium ferric cyanide reduction method. | Methanolic extract of leaf contained good content of phenolic compound (70.4 ± 2.1 mg GAE/g) which contributed as good antiradical ($IC_{50}$ value 228 ± 3.2µg/ml), chelation activity (55 ± 1.5% at 500µg), FRAP (494 ± 5.2µmol Fe (II)/g) and Potassium ferric cyanide reduction activity ($EC_{50}$ value of 978µg/ml). A correlation between the antioxidant activity (FRAP) and the phenolic content of extracts has also been drawn and found significant ($R^2$=0.965). In comparison, bark extracts possess fewer polyphenols that confer poor antioxidant potential.[69] |
| 9. *Larix gmelinii* | Bark | DPPH radical-scavenging capacity Lipid peroxidation capacity | The defatted extracts displayed a higher content of proanthocyanidins and antioxidant activity than un-defatted extracts. DPPH radical-scavenging capacity of extracts (29.88 µg $mL^{-1}$ was higher than VC (36.04 µg $mL^{-1}$), and the inhibition effect of lipid peroxidation of extracts (15%) was higher than VC (13%) and VE (11%).[70] |
| 10. | | Total phenolic content<br>DPPH radical scavenging assay<br>Superoxide anion radical scavenging assay<br>Hydroxyl radical scavenging assay.<br>Ferrous ion chelating assay | The ethyl acetate fraction of methanol extract contained the highest amount of polyphenols (47.72 ± 0.38 g gallic acid equivalents/100 g). Its DPPH scavenging and ferrous ions chelating abilities ($EC_{50}$ = 7.9± 0.1 and 1.56 ± 0.05µg/ml) were comparable to those of the positive controls, catechin ($EC_{50}$ = 7.10± 0.05 µg/ml) and $EDTANa_2$ ($EC_{50}$ = 1.27± 0.01µg/ml), respectively. It also scavenged superoxide anion and hydroxyl radicals with $EC_{50}$ values of 53.30± 5.91 and 63.12 ± 1.78µg/ml, respectively[71] |

## Conclusion

Many different human disorders are treated with medications derived from plant sources. Plant reproductive cones, roots, leaves, stems, bark, and seeds are the sources of phytochemical substances.Allopathic, homeopathic, and Ayurvedic medications are made with the phytochemicals.The purpose of medications derived from plants is to avert illnesses.Advanced technology has made a significant contribution to the development of a wide range of medications. The medications made from plant sources might come in the following forms: extracts, pills, capsules, injections, and decoctions. The medications are derived from genera that fall among the Cycadales, Confierales, Ginkgoales, and Gnetales orders. The members have a lot of secondary metabolites, which are crucial for the manufacture of pharmaceuticals.

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