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EXPLORING THE NUTRACEUTICAL BENEFITS OF *ANNONA SQUAMOSA* LEAVES FOR CHRONIC DISEASES: A REVIEW

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ABSTRACT

Natural remedies have been employed since ancient civilizations for the treatment and overall well-being of humanity. Medicinal plants offer effective solutions for disease prevention and treatment with minimal toxic side effects. Several natural medicinal plants are so ubiquitous that their therapeutic significance often goes unrecognized in daily life. The term "Nutraceuticals" is a portmanteau of "Nutrition" and "Pharmaceuticals." Nutraceuticals are food-derived products that offer medical benefits, including the prevention and/or treatment of various diseases. These nutraceutical food products can be classified into categories such as dietary fiber, prebiotics, probiotics, polyunsaturated fatty acids, antioxidants, antidiabetic agents, and other diverse herbal/natural foods. An illustrative example is the leaves of *A.squamosa*. *Annona squamosa* L., commonly referred to as custard apple, is a tropical plant belonging to the Annonaceae family. *Annona squamosa* is extensively cultivated across diverse regions, including the West Indies, Central and South America, India, and Egypt. The leaves of *A.squamosa* have demonstrated a broad spectrum of medicinal potential.

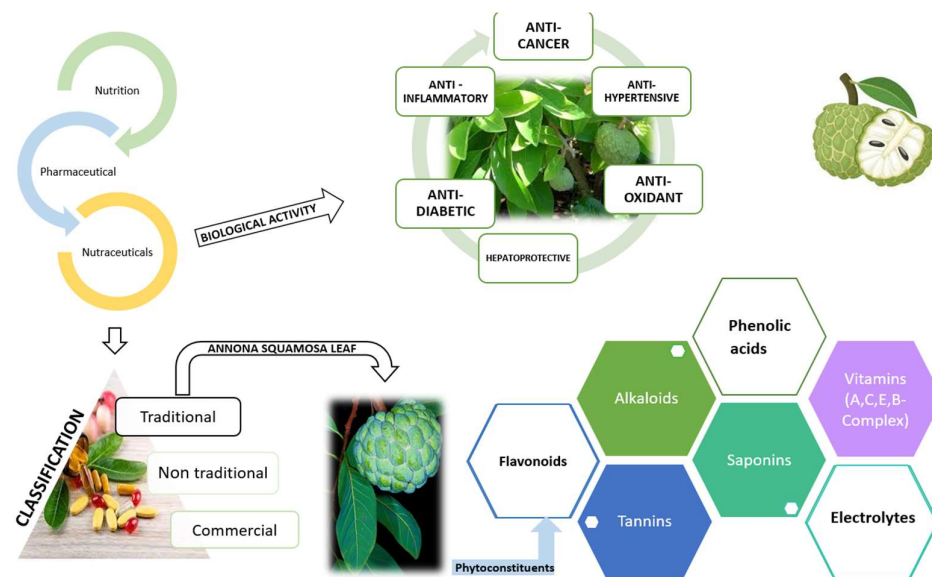
ASLs exhibit antidiabetic properties through enhanced insulin sensitivity and reduced blood glucose levels. Their antihypertensive activity is attributed to vasorelaxant and antioxidant mechanisms, while their anticancer effects arise from their capacity to induce apoptosis and

inhibit cancer cell proliferation. Furthermore, ASLs offer antimicrobial, anti-inflammatory, & hepatoprotective actions.

Consequently, ASLs present significant potential for integration into nutraceuticals—naturally derived products that provide both nutritional and therapeutic advantages. Nutraceuticals are increasingly recognized as safe, long-term alternatives for the management of chronic diseases. This article will explore the phytoconstituents, benefits, and nutraceutical applications of ASLs.

Keywords: *Annona squamosa* leaves (ASLs), phytoconstituents, nutraceuticals, antidiabetic, antihypertensive, anticancer

GRAPHICAL REPRESENTATION OF ABSTRACT



INTRODUCTION:

Nutraceuticals are defined as food-derived chemical components that, when consumed in significant quantities, exhibit favorable bioavailability and bioefficacy, thereby positively impacting health. The term "Nutraceuticals" is a portmanteau of "nutrients" and "pharmaceuticals," originating from natural sources. This term was coined by Stephen L. DeFelice, M.D., in 1989. Dr. DeFelice founded the Foundation for Innovation in Medicine in 1976 in New York, U.S., an educational

institution dedicated to fostering advancements and discoveries in medicine. He defined a nutraceutical as a food-derived substance or food component that offers health benefits, including disease prevention and treatment. Examples of nutraceuticals encompass vitamins, minerals, antioxidants, dietary supplements, fortified dairy products, citrus fruits, herbal remedies, milk, and cereals, all of which contain biologically active phytochemicals with health-promoting properties.

Health Canada defines nutraceuticals as products prepared from foods but marketed in forms such as pills, powders, or other medicinal formats not typically associated with food consumption.

All functional foods can be categorized as nutraceuticals. In India, nutraceuticals are defined as food components derived from herbal or botanical sources, utilized for the prevention or treatment of various acute and chronic health conditions [1].

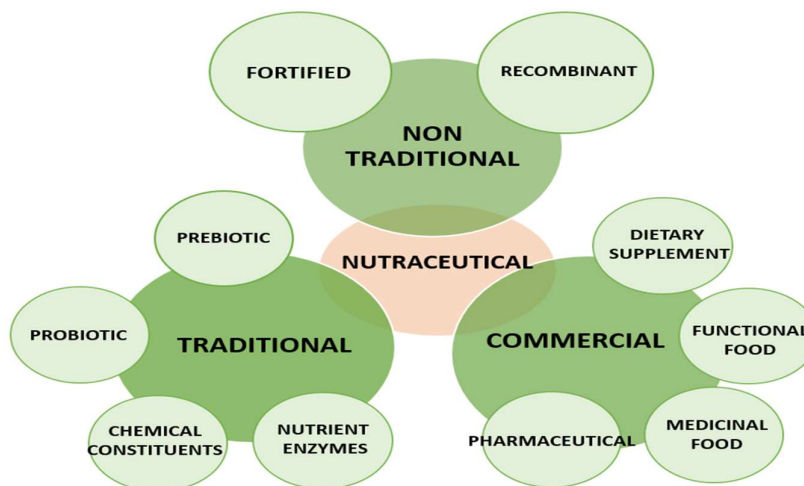


Figure 1

Why nutraceuticals are important in human life?

- 1) Nutraceuticals are used for many health problems like cardiovascular diseases, arthritis, cold, digestion, cancer prevention, high cholesterol, osteoarthritis, eye disorders, inflammation, diabetes.
- 2) Now-a-days many people are consuming nutraceuticals to stay healthy and prevent diseases because many of the people are facing with adverse drug reactions when they are taking allopathic medicines.
- 3) More consumers are worried about high healthcare costs, so they are choosing nutraceuticals to manage their health.

4) Nutraceuticals are also preferred as good option for people with low incomes or those who prefer preventing illness instead of just treating it.

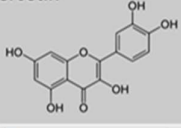
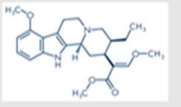
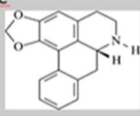
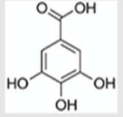
5) Nutraceuticals demonstrate significant growth potential as natural interventions for disease prevention and treatment. This paper will focus on the *Annona squamosa* (custard apple) leaf, examining its phytoconstituents, health benefits, and applications within the nutraceutical industry. *Annona squamosa*, also known as custard apple, sugar apple, or sitafal, is a versatile tree with diverse medicinal and industrial uses. The *Annona squamosa* leaves (ASLs) contain phenol-based compounds such as proanthocyanins,

encompassing 18 distinct phenolic compounds, primarily alkaloids and flavonoids. Research has explored the pharmacological activities of *A.squamosa* leaf extracts, including their anticancer, antidiabetic, antioxidant, antimicrobial, lipid-lowering, and hepatoprotective properties. Extracts derived from various components of the *Annona squamosa* plant, including its bark, roots, leaves, stem, fruit, peel, and seeds, have been historically employed in traditional pharmacological practices across diverse nations to address a spectrum of ailments, such as dysentery, epilepsy, hemorrhage, fever, and tumors. The application of *Annona squamosa* leaves for diabetes management in particular regions of India underscores how established indigenous knowledge frequently serves as a compelling foundation for contemporary scientific investigation [18].

Phytochemical Profile:

- *Annona squamosa* leaves are a significant source of diverse nutrients and bioactive compounds, including vitamins, minerals, essential oils, carbohydrates, proteins, amino acids, and various phytochemicals. Phytochemical analysis of *Annona squamosa* leaf (ASL) extracts confirms the presence of numerous phytoconstituents, such as proteins, carbohydrates, saponins, alkaloids, flavonoids, phenolics, and glycosides.
- Carbohydrates: These compounds serve as a primary energy source for the plant and are present within the leaves.
- Proteins and amino acids: Methanolic and aqueous extracts of ASLs demonstrate elevated concentrations of proteins and amino acids.
- Essential oils: Essential oils derived from ASLs exhibit notable antiparasitic and antimalarial properties.
- Vitamins and Minerals: ASLs are abundant in vitamins such as A, C, E, B1 (Thiamine), B3 (Niacin), and B9 (folic acid). Additionally, minerals including Phosphorus (P), Iron (Fe), Calcium (Ca), Magnesium (Mg), Sodium (Na), Copper (Cu), and Zinc (Zn) are present [2-4].

Table 1: Phytochemical Constituents and Pharmacological Relevance of *Annona squamosa* Leaves

NAME	CHEMICAL TEST	STRUCTURE	USES
FLAVONOIDS	<u>Ferric chloride test</u> To 2 ml of the extract, add a few drops of 10% ferric chloride solution. A green-blue or violet color is observed	Quercetin 	Anti cancer, inhibiting inflammation, anti diabetic, lowering blood pressure ,anti oxidant
SAPONINS	<u>Lead Acetate Test:</u> The formation of white precipitates when lead acetate is added to a solution indicate presences of saponin		Anti diabetic, anti cancer, anti oxidant
ALKALOIDS	<u>Dragendorff's Test:</u> An orange-red precipitate is formed when Dragendorff's reagent is added. It indicate presences of alkaloids	anonaine 	anticancer, vasorelaxant, and antiparasitic, anti inflammatory
TANNINS	<u>Gelatin Test:</u> A white precipitate forms when gelatin solution is added		Anti diarrhea, anti inflammatory, anti cancer

Methods of pharmacologicalactions:

Anticancer activity:

The circumvention of apoptosis continues to be a defining characteristic of cancer progression and a significant obstacle to successful therapeutic interventions. Given this, the apoptosis-inducing capabilities of *Annona squamosa* leaf (ASL) extracts present a compelling natural alternative to traditional cancer treatments. Abundant in various phytochemical components such as flavonoids, acetogenins, saponins, and alkaloids, ASL has exhibited substantial anticancer activity in both *in vitro* and *in vivo* research. ASL extracts have demonstrated potent cytotoxicity against a range of cancer cell lines, including MCF-7 (breast), MDA-MB-231 (triple-negative breast), HeLa (cervical), and WiDr (colon). These effects are predominantly facilitated

by the induction of oxidative stress, activation of the mitochondrial pathway, and the modulation of crucial apoptotic genes such as Bax, Bad, Bcl-2, and Caspase-3. Additionally, nanoparticle-based delivery systems, including silver nanoparticles (As-Ag NPs) and chitosan-integrated formulations, have demonstrated improved efficacy by promoting cell cycle arrest (G1 or G2/M phase), reactive oxygen species generation, and apoptosis. These results substantiate the traditional application of ASL in ethnomedicine and underscore its contemporary significance as a basis for developing secure, natural, and economical anticancer treatments [5].

Antihypertensive:

Custard apple fruit and its leaves are rich in potassium and magnesium, both of which are instrumental in blood pressure

regulation. Potassium contributes to the equilibrium of sodium levels within the body, while magnesium is crucial for maintaining a consistent heartbeat and preventing arrhythmias. Furthermore, animal studies, specifically those conducted on rats, have demonstrated that extracts from custard apple leaves can reduce the erythrocyte sedimentation rate (ESR).

Antioxidant properties:

Custard apple leaf is rich in antioxidant activity. It helps in protecting our body against oxidative stress and also reduces the chronic diseases. The mechanism of antioxidant activity entails the inhibition of lipid peroxidation, a process in which free radicals target lipids within cell membranes, resulting in cellular damage. Yang *et al.* (1970) demonstrated the antioxidant potential of *Annona squamosa* leaves in rat brains. *In vitro* assays were utilized to assess the free radical scavenging capacity of the ethanolic leaf extract. At a concentration of 1000µg/ml, the extract demonstrated robust antioxidant activity, exhibiting 99.07% scavenging of ABTS radical cation, 89.77% of 1,1-diphenyl-2-picrylhydrazyl (DPPH) radicals, and 73.64% of nitric oxide radicals. Conversely, the extract displayed only moderate activity against superoxide radicals and lipid peroxidation, as evaluated using rat brain homogenates.

In vivo studies conducted on streptozotocin (STZ)-induced diabetic rats demonstrated

that daily oral administration of an aqueous leaf extract for 30 days led to significant physiological improvements. This extract proved beneficial in reducing blood glucose levels, lipid levels, and lipid peroxidation, while also increasing plasma insulin levels. These findings indicate that the aqueous extract supplement effectively manages blood sugar levels, enhances plasma insulin production, improves lipid profiles, and is instrumental in preventing diabetic complications through its impact on lipid synthesis and antioxidant systems in diabetic rats [6].

Hepatoprotective activity:

Elevated levels of liver enzymes such as SGOT, SGPT, and ALP are indicators of liver damage. Some studies have demonstrated that *Annona squamosa* leaf extract can reduce the levels of these enzymes. Saleem *et al.* (2008) tested the hepatoprotective potential of aqueous and alcoholic extracts of ASLs on Wistar rats. Hepatotoxicity was experimentally induced using isoniazid and rifampin with silymarin serving as the standard reference drug. Biochemical analysis that treatment with *A. squamosa* extracts resulted in significant reduction in total bilirubin levels a significant increase in total protein and a notable decrease in liver enzymes such as SGOT, SGPT, and ALT. In the histopathological study, the hepatotoxic group exhibited hepatocytic necrosis,

centrilobular inflammation, and portal triaditis, the extract-treated groups showed minimal inflammation, moderate portal triaditis, and preserved lobular architecture. The study concluded that *Annona squamosa* leaf extracts did not completely reverse the liver damage, they were effective in limiting the hepatotoxic effects of isoniazid and rifampin [7].

Anti-bacterial and wound healing activity:

The leaves underwent exhaustive extraction utilizing a Soxhlet apparatus with a gradient of solvents, specifically petroleum ether, solvent ether, chloroform, alcohol, and chloroform water. All five resulting extracts were subsequently evaluated for antibacterial activity via the cup plate method. Notably, the petroleum ether, alcoholic, and chloroform water extracts demonstrated the most significant zones of inhibition. Furthermore, the petroleum ether extract exhibited superior wound healing capabilities [8].

Anti- arthritic, Anti- inflammatory and Analgesic activity:

Arthritis was induced in Sprague-Dawley rats by injecting into the metatarsal footpad using complete Freund's adjuvant (CFA). The therapeutic efficacy of the extract was evaluated by assessing hind paw swelling, body weight, and biochemical markers, including AST, ALT, and total protein, in conjunction with histopathological analysis

of knee joints. Histological examination confirmed reduced neutrophil infiltration, pannus formation, and bone erosion. Additionally, the extract exhibited dose-dependent analgesic and anti-inflammatory effects, comparable to standard drugs like pethidine sulfate and indomethacin [9].

Larvicidal activity:

We investigated the potential of ethanolic leaf extracts from *Annona squamosa* as an environmentally friendly and biodegradable larvicidal agent for mosquito control programs. Our study demonstrated both larvicidal and growth-regulating activities against *Anopheles stephensi* and other mosquito species [10].

Insecticidal activity:

Ethanolic leaf extracts were found to contain various bio-organic compounds effective against *Sitophilus oryzae*. The ethanolic extract exhibited significant insecticidal properties [11].

Anti-diabetic property:

So, they gave this ethanolic extract to regular rats, diabetic rats (the STZ kind), and diabetic rabbits (the alloxan kind) at different amounts. When they gave 350 mg/kg to normal rats, their fasting blood sugar dropped by 6.0%, and their peak blood sugar during the glucose tolerance test went down by 17.1%. For the alloxan-induced diabetic rabbits, that same dose lowered their fasting blood sugar by 26.8% and made their glucose tolerance way better, by 38.5%

and 40.6% during the test. And get this, in the STZ-induced diabetic rats, their fasting blood sugar went down by 13.0%, and their glucose tolerance improved by 37.2% and 60.6% during the test. They also checked out the watery extract from *Annona squamosa* roots at 250 mg/kg and 500 mg/kg in STZ-induced hyperglycemic rats to see if it helped with diabetes. That treatment really brought down their blood sugar, from 285.52 mg/dL to 208.81 mg/dL, which totally backs up that this plant could be good for diabetes [12].

Anthelmintic activity:

We investigated the anthelmintic activities of *Annona squamosa* leaf extracts through studies utilizing hexane, ethyl acetate, and ethanolic extracts of the crude drugs at varying concentrations. These

investigations encompassed the determination of paralysis time and death time [13].

Mosquitocidal activity:

The *Annona squamosa* Leaf extract demonstrated significant insecticidal activity suggesting that *Annona squamosa* possesses strong mosquito-killing properties and could serve as a promising source of larvicidal agents. Among the tested extracts, the ethyl acetate (EtOAc) fractions exhibited the highest efficacy, achieving 90–100% larval mortality at a concentration of 50 ppm. Additionally, extracts from *Annona* plants collected in Brazil showed larvicidal activity against *Aedes albopictus*, *Culex quinquefasciatus*, and *Anopheles stephensi* [11].

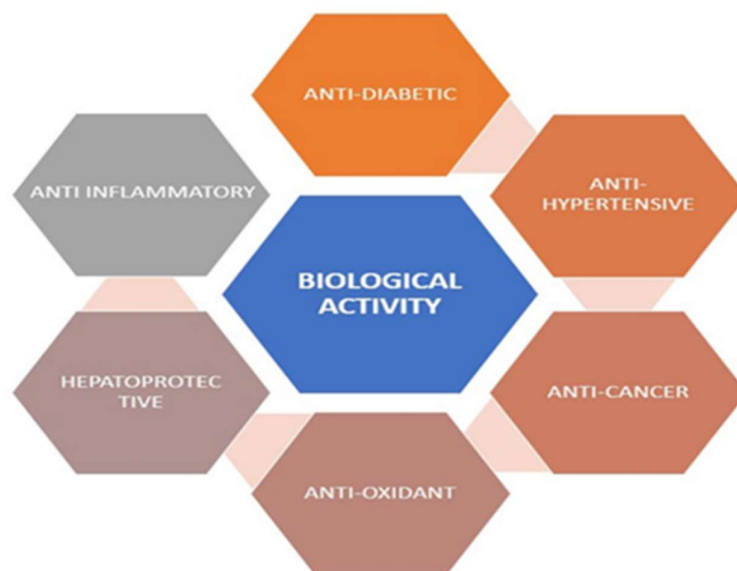


Figure 2

Table 2: Recent pharmacological studies of *Annona squamosa* leaves which possess multiple bioactivities supported mainly by *in-vitro* and animal studies, though further standardization, toxicity evaluation, and clinical trials are required to confirm their therapeutic relevance

Pharmacological activity	Evidence type	Isolation/Extraction techniques	Methodology	Results /Findings	Reference
Anticancer activity	<i>In-vitro</i> cancer cell lines (cervical) + phytochemical profiling.	Methanol extraction (Soxhlet / maceration) → solvent partitioning → column chromatography → fraction testing.	Methanolic leaf extract screened against cervical cancer cell lines; cell viability and apoptosis assays.	Showed anticancer activity against cervical cancer cells (reduced viability, apoptosis markers). Authors reported 15 compounds in active methanol extract with notable cytotoxicity.	[19]
		Methanolic / ethanolic leaf extracts prepared → fractionation → active fractions tested.	MTT/SRB cytotoxicity, wound-healing assays, apoptotic protein (Bax/ Bcl-2/ Caspase) analysis, cell morphology.	Leaf extracts reduced proliferation and migration of breast cancer cells and activated apoptotic signaling.	[20]
		Crude extraction (petroleum ether / chloroform / methanol / aqueous) → fractionation → column chromatography.	Solvent extracts (various polarity) tested by MTT/SRB or similar antiproliferative assays; apoptosis markers and morphology assessed.	Several solvent extracts (esp. nonpolar fractions / seed extracts) showed strong antiproliferative activity against multiple cell lines.	[21]
Antihypertensive activity	<i>In-vitro</i> vascular pharmacology (isolated rat aortic rings) + chemical isolation.	Leaves → solvent extraction → chromatographic purification → structure ID by NMR/MS.	Isolated rat thoracic aorta pre-contracted with phenylephrine; concentration-response relaxation measured; endothelial dependence tested; mechanistic probes for Ca ²⁺ influx and NO involvement.	The newly identified lignin (esquamosan) produced concentration-dependent vasorelaxation via inhibition of extracellular Ca ²⁺ influx through voltage-dependent / receptor-operated Ca ²⁺ channels, with a partial contribution from increased NO.	[22]
Antioxidant activity	<i>In-vitro</i> antioxidant assays + <i>in-vivo</i> oxidative-stress markers in HFF rats	80% ethanol extraction of powdered leaves; phytochemical profiling by HPLC/LC-MS showing rutin, proanthocyanidins and related polyphenols.	<i>In-vitro</i> : DPPH/ABTS and antiglycation assays; <i>In-vivo</i> : HFF rats measured plasma oxidative stress markers, DPP-IV, GLP-1.	80% ethanol extract showed strong <i>in-vitro</i> radical scavenging and antiglycation activity; in HFF rats EEAS reduced DPP-IV, improved active GLP-1 and markers consistent with reduced oxidative stress.	[23]
Hepatoprotective activity	Animal trails	Aqueous & alcoholic extract; Soxhlet extraction	Isoniazid + rifampicin hepatotoxic rat model; silymarin control; biochemical markers (SGOT, SGPT, ALP, bilirubin)	Significant reduction in SGOT/SGPT/ALT; improved total protein; preserved liver histology but not full reversal	[7]
Antimicrobial & Wound healing	<i>In-vitro</i> disc diffusion, animal wound healing	Soxhlet → serial solvent extraction	Soxhlet extraction with petroleum ether, ether, chloroform, alcohol;	Petroleum ether & alcoholic extracts showed maximum inhibition; petroleum	[8]

			cup-plate diffusion assay	ether best for wound healing	
Anti-arthritis /Anti-inflammatory/ Analgesic	<i>In-vivo</i> (formalin test, TNF-pleurisy, CFA arthritis) + <i>in-vitro</i> cytokine assays.	Methanolic extraction of leaves; chromatographic isolation of palmatine; structural confirmation by NMR/MS; bioassay-guided attribution of activity to palmatine.	Formalin pain test (early & late phases), carrageenan paw edema, CFA-induced arthritis; behavioral pain scoring, paw volume, histology; assays for TNF- α and related cytokines.	Showed dose-dependent analgesia, reduced edema and arthritic pathology, and suppressed TNF- α mediated signaling.	[24]
Larvicidal activity	<i>In vitro</i> (larval bioassay)	Leaf extraction using aqueous, ethanol, and hexane solvents.	3rd instar larvae exposed to aqueous, ethanol, and hexane leaf extracts at various.	Hexane extract showed highest larvicidal potency among the three extracts.	[25]
Insecticidal activity	<i>In vitro</i> insect toxicity assay (leaf feeding insects)	Ethanolic leaf extract (95% ethanol maceration).	Insects exposed to various concentrations (1, 10, 100, 1000 ppm) of ethanolic leaf extract	Extract showed insecticidal activity- supports that <i>A.squamosa</i> has broad spectrum insecticidal potential beyond just mosquitoes.	[26]
Mosquitocidal activity	<i>In-vitro</i>	Ethyl acetate fractionation; isolation of annotemoyin-1	Larval mortality bioassays; EtOAc extract fractions	90–100% mortality at 50 ppm; active against <i>Aedes</i> , <i>Culex</i> , <i>Anopheles</i>	[11]
Anthelmintic activity	<i>In-vitro</i> (earthworm) + <i>in-silico</i> docking	Methanolic extraction; crude extract used; no advanced fractionation / purification.	Methanol leaf extract tested on <i>P. posthuma</i> at 10, 25, 50 mg/mL; paralysis & death time recorded.	At 25 mg/mL, extract caused paralysis (~11.8 min) and death. Docking suggested that leaf flavonoids (quercetin, rutin) may bind β -tubulin.	[27]
Antidiabetic activity	<i>In-vivo</i> (rodent)	Hydro alcoholic leaf extract (HAEAS).	Alloxan-induced diabetic albino rats; oral HAEAS (350 & 700 mg/kg) for 28 days; blood-sugar measurement.	Hydro alcoholic leaf extract produced dose-dependent fall in blood sugar levels compared to diabetic control; efficacy comparable to standard (Glibenclamide).	[28]

DISCUSSION:

Nutraceuticals are effectively bridging the divide between food and medicine. As Hippocrates aptly stated, "Let food be thy medicine and medicine be thy food." This adage underscores the profound impact of diet on health maintenance and improvement. The long-term use of synthetic medications for chronic conditions has unfortunately led to various side effects, primarily due to the accumulation of toxic drug metabolites over time. This in turn leads to hepatic and renal impairment

because of overworking to metabolize and excrete chemicals. Nutraceuticals derived from natural sources are much safer and come with milder side effects proving highly beneficial in long-term health management, prevention, and overall well-being. They support the body's natural physiological processes, rather than just masking symptoms whereas Long-term use of many synthetic drugs requires careful monitoring due to potential for cumulative toxicity, development of resistance (e.g., antibiotics), or dependence.

However, the challenges being, nutraceuticals are often regulated as dietary supplements, not drugs. This means that they generally don't undergo the same strict pre-market testing for efficacy, safety, and quality. Lack of standardization can lead to inadequate amount of active ingredients, poor bioavailability, or even contaminants which often mislead the consumers with exaggerated or unproven health claims in marketing [12]. While *in vitro* and animal studies are promising, there's a significant need for more large-scale, well-designed, randomized controlled human clinical trials [16, 17].

Market Growth:

Nutraceuticals are integral to various industries, including pharmaceuticals, food and beverages, animal feed supplements, and personal care products. The global nutraceutical market, valued at an estimated USD 591.1 billion in 2024, is projected to reach approximately USD 919.1 billion by 2030, demonstrating a compound annual growth rate (CAGR) of 7.6% from 2025 to 2030. In 2024, North America accounted for over 31.8% of the total global revenue. Looking forward, the U.S. nutraceuticals market is anticipated to grow at a CAGR of 6.2%, while the European market is expected to exhibit a slightly higher CAGR of 6.9% during the same period [15].



Figure 3

CONCLUSION:

Nutritional deficiencies are most prevalent in developing nations. In India, iodine-fortified salt and folic acid-fortified wheat flour have been utilized for several years to combat Goiter and Anemia, respectively. The demand for nutraceuticals in India has experienced a substantial increase since 2020. The Indian nutraceutical market is undergoing significant evolution and is projected to reach USD 18 billion by the close of 2025, a considerable rise from USD 4 billion at the end of 2020. This represents a growth exceeding fourfold within a five-year period. The COVID-19 pandemic has notably contributed to a surge in the sales of nutritional supplements, with a rapid escalation in the emphasis on bolstering immunity. As the saying goes, “prevention is better than cure”, the newer generation are all about preventing diseases by leaning towards the organic plant-based foods, nutritional supplements and superfoods. To improve the nutraceutical growth so many technologies are being developed. This is where nutrigenomics comes into the picture. Nutrigenomics mainly focuses on how nutrients interact with genes, influencing gene expression, protein synthesis and metabolic pathways. This has opened gates for personalized or tailored nutraceuticals for individuals, which improves the usage of nutraceuticals. The increasing human life span has led to a rise in chronic and age-

related diseases, including neurodegenerative disorders, diabetes, and various cancers. Concurrently, escalating healthcare costs and a growing emphasis on preventive health have redirected global attention toward safer, more sustainable alternatives, specifically "Nutraceuticals." These bioactive food-based products are now recognized not only for their nutritional value but also for their therapeutic potential. Among them, *Annona squamosa* particularly its leaves, stands out as a promising natural source with potent pharmacological properties. Presence of flavonoids, alkaloids, saponins, vitamins and essential minerals, the leaf extracts exhibit wide ranging activities like hepatoprotective, anti-diabetic, anti-oxidant, anti-cancer and even insecticidal activities. However, despite encouraging in vitro and in vivo results, challenges remain in translating these findings to human health outcomes. Issues of regulatory oversight, lack of standardization, and limited clinical evidence continue to hinder the full-scale integration of nutraceuticals into mainstream medicine. The bioavailability of nutraceuticals, its toxicities, animal & human trials, improved quality control and efficacy and safety are essential to study to bridge gap between traditional knowledge and evidence based studies. So as a pharmacist we should take the initiative to conduct more researches

about the nutraceutical and improve patient specific life.

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