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Therapeutic potential of *Agave* spp. in modern healthcare: A comprehensive review

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Abstract

Agave, a succulent plant from the Asparagaceae family, is gaining attention in modern healthcare due to its diverse therapeutic properties like anti-inflammatory, antimicrobial, anticancer, antiulcerogenic, antihypertensive and antidiabetic. This makes *Agave* an important resource in the fields of pharmacology, nutrition and social health. These therapeutic advantages are due to the occurrence of bioactive substances found in *Agave* species, such as flavonoids, saponins, terpenes, steroids, glycosides, *etc*. It also possesses antioxidant qualities that aid in defending against oxidative stress and related illnesses. *Agave* extracts have shown potential in the treatment of arthritis, hepatotoxicity, excessive blood pressure, *etc*. These properties of this plant help in the invention of various drugs that dominate conventional drugs. *Agave* has been traditionally used in wound healing, digestive issues and as a natural remedy for skin diseases. Thus, we can use it in cosmetics also. Despite these promising results, extensive research is needed to explore the underlying mechanisms, enhance extraction methods and assess safety and clinical effectiveness. The expanding interest in plant-based therapies underscores the potential of *Agave* as a valuable resource in modern pharmacology and integrative medicine. Further exploration of bioactive compounds of *Agave* could make way for new plant based therapies that complement or enhance conventional treatments, especially in an era of sustainable and integrative medicine.

1. Introduction

Agave crop is a succulent plant that flourishes in semiarid or arid environment and belongs to the family Aspargaceae. *Agave americana L., A, tequilana, A. attenuata* and *A. sisalana* are some of the commonly grown species of *Agave*. It is a group of monocots growing in a harsh environment. *Agave* is cultivated across the American continent. It needs low humidity soil, bright light, temperatures between 15° to 25°C and an altitude of between 1700 and 2400 meters above sea level. Almost 200 species are there in this genus. Approximately 75% of the species in the genus are found in Mexico, which is why it is regarded as an *Agave* diversity center. The family genera are renowned for their succulent and xerophytic species, typically producing massive rosettes of sturdy and meaty leaves. The rosettes of Agavaceae plants are distinguished by their thick, stiff and rigid leaves, which frequently have marginal teeth. While some flowering species of *Agave* emit subtle scents that attract insects, many produce musky scents that draw bats and pollinate them (Kablan *et al.,* 2024). The economic foundation of *Agave* plants can be improved if, spent biomass is turned into items suited for use in food, ensilage, forage, agriculture, energy, medicine, the environment, cosmetics, textiles, *etc*. (Perez *et al.,* 2020). In spite of significant annual fluctuations, Brazil has continued to produce *Agave* fiber for the past 60 years. But during the past 30 years, China has reported the highest yield per unit land area of any nation (Davis, 2022). *Agave* species have many uses in traditional medicine, such as diuretics, laxatives and remedies for cancer, psoriasis, trauma, snake bites, syphilis, sores, scurvy, wounds, fractures, rheumatoid arthritis, limb paralysis and postpartum abdominal inflammation.

Many *Agave* species are employed as effective anti-inflammatory drugs or therapeutic herbs in traditional medicine. *Agave* has been utilized historically as a raw material for culinary and medical reasons. *Agave* is used in conventional processing to produce syrups high in carbohydrates that can be used directly or as a substrate to make spirits and other hydrolyzed fermented products. Significant concentrations of inulin, a crucial chemical with probiotic function, can build up in *Agave* plants (Santos *et al.,* 2012). *Agave* syrup possesses antioxidant and anticancerogenic qualities. Studies have demonstrated the antifungal and antibacterial qualities of this plant. Furthermore, *Agave* base leaves contain fructans up to 16%. Stem and leaf bases can be utilized to commercially produce fructans and long-chain inulin, which can be employed as vaccine adjuvants in the pharmaceutical business (Bouaziz *et al.,* 2014). In arid areas that experience repeated droughts, grazing animals have been fed the *Agave* plant. This plant has a lot of saponins, which are known to be antinutritional, anticancer, antifungal and anti-inflammatory. Since saponins are not readily soluble in water, other methods must be developed as a means of extracting these compounds from plants (Santos *et al.,* 2012). *Agave* lignocellulosic materials are abundant in polysaccharides like xylan, which is a cost-effective source for the synthesis of xylo-oligosaccharides (XOS). They also contain

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significant amounts of sugars and fructo-oligosaccharides (FOS), such as inulin. These substances are resistant to stomach acidity, susceptible to intestinal bacterial fermentation and capable of boosting the viability of beneficial microorganisms. Prebiotic functional ingredients found in *Agave* have a lot of potential for use in the creation of wholesome and nourishing products. This is because *Agave* contain a lot of dietary fiber and beneficial substances. Thus, utilizing *Agave* residues is a potentially useful tool for raising the caliber and nutritious content of food (Marquez *et al.,* 2023).

Leaves, sap, root, fiber, *etc*., of *Agave* have various medicinal properties. Since pre-Hispanic times, they have been used in ancient Mexican treatment to cure a wide range of ailments. Research on the key ingredients that give *Agave,* their medicinal properties has grown throughout time. *Agave* plants are gathered and grown for their floral scape, stem and foliar bases, leaves and sap, flowers and flower buds, which are used to make a variety of dishes. These foods frequently aid in their survival under harsh circumstances. Nutraceutical components such as saponins, fructans, inulin, dietary fiber, phenolic compounds and antioxidants, amino acids and minerals have all been used to study the role of *Agave* in human nutrition (Santiago *et al.,* 2023). In this review, we have discussed the bioactive compounds of *Agave*, minerals in *Agave*, therapeutical applications of *Agave* which includes anticarcinogenic, anti-inflammatory, antihepatotoxic, antidiabetic, antiarthritics, antihypertensive, antiparasitic and immunomodulatory effect, the importance of *Agave* syrup, antimicrobial and antioxidant properties of *Agave*.

2. Bioactive compounds of *Agave*

Agave has been utilized to treat oxidative stress and a variety of bacterial illnesses (Ahumada *et al.,* 2013). Several studies have shown that it has antifungal, anti-inflammatory, immunomodulatory, antiparasitic and antihypertensive properties. *Agave* plants contain a variety of secondary metabolites, including steroids, triterpenes, volatile coumarins, tannins, flavonoids, free anthracene derivatives, alkaloids, reducing sugars and cardiotonics. Among the plants with the most phytochemical variety is *A. ornithobroma*. In addition to the substances listed above, steroidal saponins, flavonoids and tannins also exhibit bioactive action. Antioxidant, antitumoral and antibacterial properties are attributed to tannins and flavonoids. Certain organic extracts from *Agave* species have been shown to have antibacterial activity against *Shigella dysenteriae, Enterococcus faecalis, Salmonella enterica typhi, Escherichia coli, etc*. *A. tequilana* has shown particularly strong antibacterial activity. Among other species, *A. rzedowskiana* exhibits the release of antioxidant activity (Ahumada *et al.,* 2013).

2.1 Fructans

Fructans are natural sugars that are found in *Agave* plants. Blends of fructose polymers with varying degrees of polymerization make up these polysaccharides. In addition to serving as osmo-protectants during drought, these photosynthetic carbohydrates serve as a reserve source of energy for several metabolic functions in *Agave* plants. Crushing *Agave* pine, followed by hot water extraction, removing impurities, making syrup concentration and syrup spray drying, is the most common technique for producing *Agave* fructan powders. Additionally, the process of extracting, cleansing and drying operations might affect the quality and yields of *Agave* fructan powders by affecting their physical and chemical stability. Because of its technological qualities and positive health effects, *Agave* fructans are now being used as functional additives in a variety of food products. *Agave* fructans are nutritious components that support the development of good bacteria, control blood sugar, act as immunomodulatory agents, reduce obesity and overweight-related health issues, enhance calcium absorption and have chemoprotective and antioxidant properties. *Bifidobacterium* and *Lactobacillus* gut bacteria in our bodies use *Agave* fructans to proliferate and enhance several host biological activities (Espinosa *et al.,* 2021).

2.2 Inulin

Inulin, a fructan that is composed of fructose molecules connected by β-(1-2) fructose-fructose bonds, is one of the most significant carbohydrates found in an *Agave*. The technological application of inulin is predicated on its ability to substitute sugar, fat and texture. Inulin appears to be especially appropriate for replacing fat in dairy products with low fat content since it may enhance the mouthfeel. Additionally, inulin was employed to enhance the nutritional value and rheological qualities of food, allowing it to be categorized as a functional food. There is ample proof of its ingestion and detrimental consequences on health. Patients with type 2 diabetes showed lower levels of insulin, glucose, tumor necrosis factor-alpha (TNF-α), C-reactive protein and lipopolysaccharides (LPS) in their plasma after consuming 10 g of inulin daily for eight weeks. LPS is a crucial part of the outer cell wall of Gram-negative bacteria and is a trigger for the metabolic decrease seen in type 2 diabetes and obesity (Dehghan *et al.,* 2014). Inulin-type fructans are indigestible carbohydrates that are structured into soluble, fermentable and non-viscous fibers. By reducing firmicutes and increasing *bifidobacteria* and *bacteroidetes*, it can alter the composition of microbiota in the gut and diminish the dysbiosis or bacterial imbalance responsible for diabetes and obesity (Santiago *et al.,* 2023). The microbiota of the gut contains the helpful bacteria called *Akkermansia muciniphila*, which is reduced in obese and diabetic individuals. *Akkermansia muciniphila was* more prevalent in both clinical and *in vivo* investigations when inulin was consumed (Zhou, 2017). The daily oral supplementation of 10^{10} bacteria of *Akkermansia muciniphila* for three months improved insulin sensitivity and reduced inflammatory markers and cholesterol levels in a human study including thirty-two adults who have an excessive amount of body fat, which is a risk to health with insulin resistance (Depommier *et al.,* 2019). Inulin is regarded as a soluble fiber that can be added to a variety of food products because, according to its chemical makeup, it is neither hydrolyzed nor absorbed in the small intestine. In certain formulations, it can be used in place of sugar due to its mild sweetness and characteristics that are comparable to those of sucrose. *Bifidobacteria* are thought to have health promoting properties because inulin promotes their proliferation. Inulin has numerous other health benefits related to diabetes, cholesterol metabolism, preventing cancer, and antiulcer action. Since inulin consumption is linked to lower levels of cholesterol and triglycerides, there is enough proof of its antihyperlipidemic action nutrition. Low density lipoprotein cholesterol (LDL-c) was reduced in individuals with initially elevated LDL-c levels when 18 g/day of inulin was consumed on a low-fat diet (Santiago *et al.,* 2023).

2.3 Saponins

Saponins are metabolites that possess both hydrophilic and hydrophobic characteristics. 86 glycosylated saponins and almost 28 steroidal saponins have been isolated from these plants, although the number is continually rising. Saponins are categorized as steroids (C27) and triterpenoids (C30) and consist of a sugar moiety that includes glucose, glucuronic acid, galactose, rhamnose, xylose or methylpentose, connected to an aglycone that is not polar (sapogenin). Monodesmosidic saponins are substances in which the oligosaccharide is typically linked at the C3 position. Didesmosidic saponins, on the other hand, have an extra sugar unit connected at C26 or C28. The majority of the bioactive substances found in *A. americana* extract are saponins, which make up 80 g diosgenin equivalent kg/dry weight. On the other hand, several other investigations have separated and described distinct saponins from extracts of *Agave* (Lopez *et al.,* 2018). *A. brittoniana* and *A. sisalana* extracts contain saponins called spirostane. Furostanol and spirostanol saponins can be isolated from *A. macroacantha* and *A. utahensis* extracts. Furthermore, magueyoside and dongnoside E saponins have been identified in *A. offoyana* and *A. sisalana*, respectively. It is possible to separate two steroidal saponins from *A. lophantha;* they are monodesmosidic spirostanoside and a didesmosidic furostanol glycoside. These substances have demonstrated hemolytic, cytotoxic, antifungal, anti-inflammatory and anticancer properties (Sidana *et al.,* 2016). Santos *et al.* (2016) used purified fractions of tetra-glycosylated steroidal saponins and penta-glycosylated steroidal saponins from *A. salmiana* sap to study anticancer efficacy against lung cancer cell lines. Several saponins, including hecogenin, tigogenin, and agavasaponin E and H, have been determined and recognized by *A. americana*. Compared to the aqueous extract, hecogenin and tigogenin which were separated from *A. americana,* had stronger anti-inflammatory effects. Additionally, the leaves contain substances that have anticancer properties. The oral administration of *A. americana* extract to sheep at varying saponin dosages has antiprotozoal properties and can also reduce the levels of glucose and cholesterol in the blood (Babu *et al.,* 2015).

Steroidal saponins have been shown to have gastroprotective properties. According to a recent study, the presence of various glycoside chain substitutions did not cause hemolytic changes in stomach tissue when isolated glycosylated steroidal saponin from *A. angustifolia* was present. In addition to reducing cholesterol affinity for the erythrocyte membrane, this structural characteristic also provided cell protection and non-cytotoxic damage to these cells (Pereira *et al.,* 2017). The impact of a methanolic extract and a saponin-enriched fraction of *A. seemanniana* leaves was evaluated in another trial; both studies showed comparable reductions in ulcer severity to ranitidine at 50 mg/kg. Nevertheless, they were only effective at 200 mg/kg. At a dose of 100 mg/kg, the extracts exhibited analgesic and anti-inflammatory properties. The therapeutic effect was comparable to that of aspirin (100 mg/kg) and indomethacin (20 mg/kg) at this level of dose.

Agave has two distinct steroidal sapogenins, namely spirostanol (1-27) and cholestane (Agavegenin D-28). A tetrahydropyran ring and a tetrahydrofuran ring joined to the C-22 position in a spiral fashion comprise the skeleton of spirostanol. The leaves, callus cultures, leaf juice, flowers and rhizomes of *Agave* are the sources of spirostanol sapogenins. *Agave* spirostanol sapogenins vary from one another in the following ways: 1) the quantity and form of hydroxyl moieties connected to the parent nucleus; 2) with or without a carbonyl group at C-12; 3) with the arrangement of H at C-5 and C-25 and 4) with or without unsaturation in rings B or C (Ingawale, 2020).

2.4 Phytosterol

Phytosterols are hydrophobic molecules with cholesterol as the basic structure. Instead of existing in free form in plants, these metabolites can be found as conjugates of acyl groups, glycosides and esters. A study found that using extraction through ultrasound technology in the stem of *A. angustifolia* resulted in higher yields of β-sitosterol-D-glycoside in a shorter time than maceration extraction. Additionally, *A. tequilana* (50 mg/kg) increased the synthesis of interleukin-10 (IL-10), a cytokine that controls the auto-immune response. Gas chromatography-mass spectrometry (GC-MS) was used to identify and quantify phytosterols and terpenes linked to this activity, including phytol (0.1615), β-sitosterol-glycoside (0.1995), cycloartenol (0.019) and stigmasta-3,5-dien-7-one (0.0285) mg/g extract (Gutierrez *et al.,* 2017). *Agave* extracts have also been found to contain terpenes. In comparison to maceration extraction, the pina of *A. angustifolia* exhibited high extraction yields of β-sitosterol-D-glycoside in rapid process time. Hernandez *et al.* (2014) used a mice model with ear edema inflammation initiated by tissue plasminogen activator (TPA) to examine the anti-inflammatory properties of this acetone fraction *A. angustifolia*. *A. salmiana* contains terpenes, including trans-nerolidol, 4-terpineol, p-cymene, limonene, linalool, geraniol, *etc*. The terpenes p-cymene, 5α-trans-ocimene, geraniol, limonene, linalool, 5α-terpineol and trans-nerolidol were found in the extract of *A. angustifolia*. A beverage made from *A. salmiana* had significant levels of limonene, 5-terpinene and 5-terpineol.

2.5 Polyphenols

The *in vivo* biological potential of polyphenols derived from several *Agave* species has been examined and assessed. Insecticidal activity against *Bemicia tabaci* was demonstrated by the hydroalcoholic extract of *A. lechuguilla*. El-Hawary *et al.* (2020) found that leaf extracts from *A. desmettiana*, *A. angustifolia, A. americana* and *A. pygmaea* have anti-inflammatory and immunomodulatory properties. In contrast, *A. pygmaea* and *A. angustifolia* had the highest immunomodulatory activity on *in vivo* inflammation models at a concentration of 200 mg/kg and reduced pro-inflammatory cytokine concentrations. It was discovered that polyphenol extraction techniques were crucial for measuring the antioxidant concentration and plant capacity. Various procedures, including microwave-assisted extraction, ultrasonic extraction and diverse extraction techniques employing various solvents and conditions, were developed for the extraction of polyphenols from various plants. The metabolomic profile of these species revealed a variety of phenolic acids, glycosylated flavonoids and homoisoflavonoids, including rutin, kaempferol, quercetin, eucomol, dyhydroeucomin, fukiic acid, sinapic acid, piscidic acid, *etc.,* and their presence was linked to these effects (Bermudez *et al.,* 2021). According to the investigations of Sahnoun *et al.* (2019), the bioactive potential is selective and varies depending on the type of isolated molecule. While p-coumaric acid was revealed to be a significant inhibitor of human α-amylase at IC_{50}: 98.8 M, with an inhibition rate 2.3 times higher than puerarin, acarbose and apigenin, which were isolated from this species. It shows larger inhibitory actions against *A. oryzae* α-amylase. Therefore, postprandial glycemia may be treated with isolated flavonoids.

Phenolic molecules with 15 carbon atoms (C6–C3–C6) make up flavonoids. Based on their structural characteristics, flavonoids are categorized as chalcones, flavones, flavonols, anthocyanidins, flavanones, isoflavones, neoflavonoids and flavanonols. Some research has used both quantitative and qualitative testing to investigate the presence of flavonoids in *Agave* extracts. Six *Agave* species (*A. schidigera, A. rzedowskiana, A. ornithobroma*, *A. tequilana*, *A. angustifolia* and *A. impressa*) were assessed for phenolic content by Ahumada *et al.* (2013). The phenolic content of these species ranged from 2.06 mg to 12.37 mg gallic acid equivalents g/dry weight. *A. angustifolia* had the lowest content, while *A. ornithobroma* had the most. *A. durangensis* extracts include a variety of flavonoids, including quercetin glycoside, kaempferol-3,7-O-diglucoside, kaempferol glycoside, kaempferol-3-O-[6-acetylglucoside]-7-O-glucoside, *etc*. The most important flavonoid in *A. americana* is kaempferol. Benzoic acid, quercetin-3-O-glycoside, cinnamic acid and kaempferol-3-O-glycoside are found in the extracts of *A. striata* and *A. lechuguilla* (Lopez *et al.,* 2018).

3. Minerals in *Agave*

Agave plants include nondigestible carbohydrates, which can impact mineral bioavailability. Bone retention and intestinal absorption of calcium and magnesium are unaffected by *Agave* fructans. Intestinal absorption of calcium takes place in distinct locations and by different mechanisms, intestinal absorption of magnesium, happens through passive diffusion from the distal area of the small intestine and the primary section of the colon. Furthermore, 850 ml of *Agave* nectar can meet the daily requirements for zinc and iron. The macro elements potassium, calcium and sodium are found in greater amounts in the meadow of *A. atrovirens*, while the microelements iron, copper, selenium and zinc are found in smaller amounts. According to a mineral analysis of *A. angustifolia* and *A. karwinskii*, the foliar tissues of these plants included nitrogen, phosphorous, potassium and calcium and the pine or foliar bases also had these elements (Santiago *et al.,* 2023). The leaves of adult *A. angustifolia* and *A. karwinskii* plants contained higher levels of nitrogen, phosphorous, potassium, calcium and magnesium than the stems, which displayed higher sulphate concentrations. The leaf tissues of *A. karwinskii* have higher concentrations of calcium, magnesium, zinc and sulphate than those of *A. angustifolia*. The macro elements potassium and nitrogen were the most prevalent in *A. salmiana* flowers, with respective concentrations of 1.6 and 1.72 g/100 g of dry matter, followed by phosphorous in 0.32 g/100 g of dry matter, calcium in 0.22 g/100 g of dry matter and magnesium 0.12 g/100 g of dry matter. Comparing *A. salmiana* to other edible flowers, the amounts of iron are 86.6 mg/kg of dry matter and zinc is 46.6 mg/kg of dry matter, which is a higher quantity. People who live in unfavorable environmental conditions or have limited access to food might benefit greatly from *Agave* blossoms as a source of nutrients. For individuals in underdeveloped countries like Mexico, where diets centered on grains and cereals frequently lack micronutrients and vital minerals like iron, *Agave* provides vital elements. It was discovered that *Agave* honey had 1 mg/100 g of calcium, 0.09 mg/100 g of iron, 1 mg/100 g of magnesium, 1 mg/100 g of phosphorous, 4 mg/100 g of potassium, 4 mg/100 g of sodium and 0.01 mg/100 g of zinc (Santiago *et al.,* 2023). Thus, the minerals in *Agave* contribute a lot to enhance human health.

4. Therapeutical applications of *Agave*

Agave contains various bioactive compounds like flavonoids, saponins, terpenes, steroids, glycosides, *etc*. These phytochemicals are the reason for the various therapeutic activities of *Agave* which are shown in Figure 1.

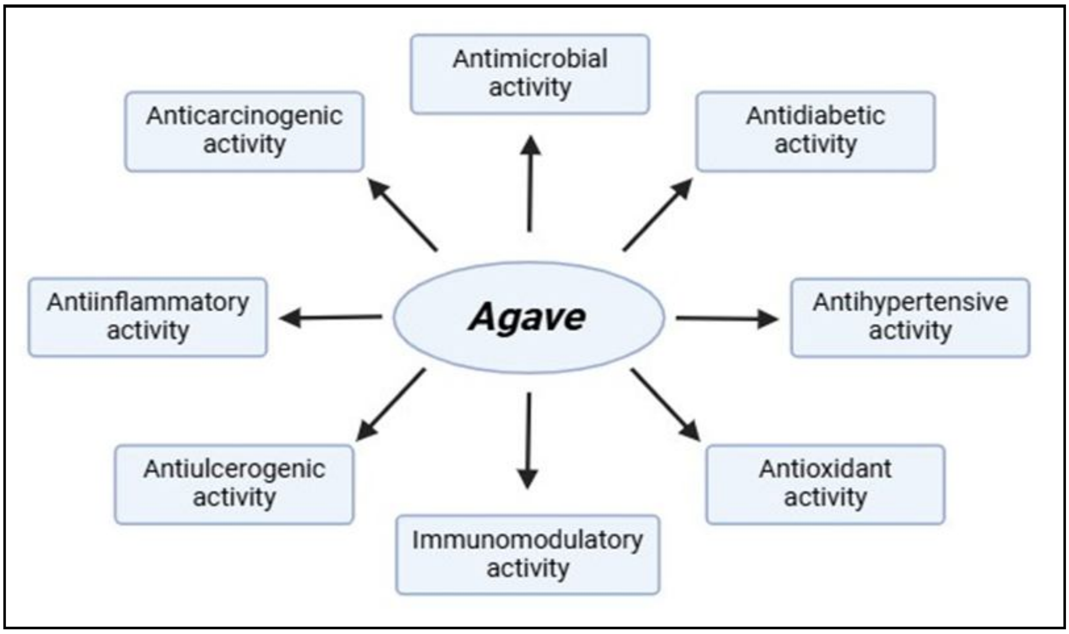

Figure 1: Therapeutical activities of *Agave*.

According to the pharmacological analysis, *Agave* leaf juice decreases blood pressure, induces abortion in pregnant animals and stimulates the intestinal and uterine muscles. *Agave* sap is used to prevent the formation of bacteria in the intestines and stomach since it has antibacterial qualities. In Northern Morocco, the juice from the leaves of this plant is used in folk medicine as a wash for skin disorders (El-Hilaly *et al.,* 2003). Syphilis is treated with *Agave* extract and it is occasionally advised for jaundice, liver illness and pulmonary tuberculosis. It has laxative properties as well.

The pharmacological characteristics of the juice include its hypotensive, emmenagogue, and uterine stimulating qualities. The plant can be consumed when baked and is also high in saccharine. In Central America, the sap of *Agave* has traditionally been used to bind different powders that are applied as wound remedies. The herb is taken internally to cure diarrhea, jaundice, constipation, gas and indigestion. *Agave* fiber soaked in water for one day can be used as a tonic and scalp cleanser for hair loss. The *Agave* root has diuretic and diaphoretic properties. The leaves are used to make the precursors of steroid drugs. Toothaches are treated with gum that is derived from the roots and leaves of *Agave*. It is applied to syphilis patients. The plant's entire sections can be collected, dried and used as needed (Debnath *et al.,* 2010). *A. cantula* is a perennial herb that grows in wastelands as well as roadsides. It is generally grown as a fencing plant as well. Many components of this plant are thought to have been utilized historically as medications for a variety of medical conditions, with each part serving a distinct function. According to folklore, this mixture has historically been used for several purposes, including as a purgative, antiscurvy, antisyphilis, antiedema, antiretention of urine and anticancer. Chemical analysis has shown several components in *A. cantula*. Hecogenin, tigogenin, sterol type glycosides and flavonoid-type glycosides are some of these constituents. Additionally, scientists have investigated the alcoholic and aqueous extracts of the plant for the possibility that they could have cytotoxic effects (Cheruku *et al.,* 2024).

Pulque is a classic fermented beverage produced from *Agave*. In Mexico during the colonial era, it was the most widely consumed fermented beverage. To enhance the beverage, other culinary components were frequently added, such as toasted leaves of maize, honey, cinnamon, brown sugar, salt, garlic and maguey worms. Nowadays, the sap or mead of *Agave* plants like *A. americana, A. mapisaga, A. hookeri* and *A. marmorata* is fermented to make pulque. The alcohol content in pulque typically ranges from 4 to 6% by volume. The distinctive flavor of this beverage is created using fermentations of alcohol, acetic acid and lactic acid. Nowadays, lactic acid bacteria, including *Leuconostoc* and *Lactobacillus*, have been shown to have antibacterial, probiotic and anti-inflammatory properties. Because of its composition, pulque is thought to have exceptional value as a probiotic and prebiotic drink. It has also been demonstrated to be helpful in the treatment of intestinal infections and gastrointestinal diseases. It is a significant source of vitamin B, ascorbic acid and iron (Santiago *et al.,* 2023).

Historically, pre-Hispanic tribes in Mexico, including the Aztecs and Mayans utilized *Agave* for their medical benefits. For instance, the Mayans applied the leaf juice of *A. fourcroydes* topically to treat wounds. On the other hand, snakebites and cutaneous and excretory skin infections were treated with the leaves and roots of *A. angustifolia*. The Aztecs extracted concentrated sap by pressing the fresh leaves of *A. potatorum, A. americana* and *A. atrovirens*. After they combined it with salt, honey, hot urine and a few other therapeutic plants. Finally, deep wounds were treated with the mixture. Some *Agave* species were domesticated by the Tarahumara indigenous people, who utilized them in therapeutic remedies that involved applying leaf juice to septic lesions. Headaches were treated with concoctions including whole leaves, while ocular diseases were treated with sap (Bermudez *et al.,* 2021).

As a treatment for jaundice, the central bud of *A. sisalana* is cooked with salt and the resulting decoction is given to patients; it is claimed to start working within 24 h. The aqueous extract of *A. attenuata* was recently tested for its ability to exhibit molluscicidal, piscicidal and larvicidal effects against *Bulinus africanus, Daphnia pulex, Oreochromis mossambicus* and *Anopheles arabiensis* (Brackenbury and Appleton, 1997). *A. potatorum* helps in wound healing and forming scar tissue. It also heals respiratory illness (Delgado *et al.,* 2014). Leaf gel extracted from *A. americana* leaves also helps with wound healing and forming scar tissue. Leaves and roots of this particular plant are used for syphilis treatment, headache, rheumatic pain, *etc*. It is also used in the treatment of gout disease (Torre *et al.,* 2018). Roots of *A. sisalana* act as antidiarrheic medicine. Meningitis and sciatica can be treated using the leaves of *A. sisalana and A. karattos* (Chaachouay *et al.,* 2020).

4.1 Anticancer properties

The mechanism of action of anticancer medications is mostly dependent on their cytostatic activity or their cytotoxic activity, which makes their toxicity a major concern. The clinical potential of these medications is limited by the inevitable occurrence of non-target damage. Numerous studies have verified the use of natural products and herbal extracts to prevent such toxicity (Sheikh Raisuddin *et al.,* 2018). *A. schottii* extracts, rich in saponins, showed anticancer efficacy against breast cancer. Concentrations of 75 and 37.5 mg/kg reduced tumor incidence by 7% and 28%, respectively. In a similar vein, an extract from *A. americana* cytotoxically affected Modified Citrus Pectin-7 (MCP-7) and Michigan Cancer Foundation-7 (MCF-7) cells (human breast cancer cells) at half maximal inhibitory concentration (IC_{50}) values of 545.9 μg/ml and 826.1 μg/ml, respectively (Anajwala *et al.,* 2010). The capacity of *Agave* extracts to function as preventative agents by lowering ROS production, redox potential and chelating chemical levels is the foundation of their anticancer action (Greay *et al.,* 2015). Furthermore, these substances demonstrated efficacy against malignant cell lines by preventing the spread of cancer. These chemicals inhibit the expression of key enzymes, including tumor necrosis factor-alpha (TNF-α), nuclear factor kappa B (NF-α), cytochrome P450 (CYP), PKs, heat shock proteins (HSPs), *etc.* (Bhalla *et al.,* 2013). According to hydrogen peroxide scavenging assays, *A. angustifolia* extract demonstrated antioxidant activity (IC_{50} value of 203.00 μg/ml) and anticancer activity (IC_{50} value of 82.70 ± 1.458 μg/ml) when compared to the standard medication, doxorubicin, which exhibits a lower inhibitory rate than the extract against the HeLa CCL-2 cancer cell line. According to Alvarez *et al.* (2023), healthy colon CRL1831 cells benefited from fructans mixes *of A. salmiana* and chicory; no cytotoxicity was observed in healthy cells as opposed to cancer cells, which is a requirement for any chemopreventive therapy. When compared to *Bifidobacterium longum* subsp. *infantis*, these fructan mixtures also improved the potential prebiotic qualities, encouraging the growth of *Lactobacillus acidophilus*. The increase in the generation of short-chain fatty acids and lactic acid also boosted the metabolic activity of these bacteria. As a result, combinations of linear and branched fructans may be a useful prebiotic and cancer colon preventive strategy (Chikara *et al.,* 2023).

4.2 Anti-inflammation properties

Agave extracts have also been demonstrated to reduce inflammation. *A. americana* extract (200 and 300 mg/kg) effectively reduced stomach mucous membrane inflammation by 50%. Furthermore, the assessed dose had no adverse effects (Peana *et al.,* 1997). *A. intermixta* extracts

(300 and 500 mg/kg) resulted in a 50% reduction in inflammation compared to the control group. Furthermore, there was a 60% reduction in inflammation when *A. attenuata* saponin 100 μg/kg was applied to vascular permeability inflammation. Dunder *et al.* (2010) discovered that *A. sisalana* extract (500 mg/kg) reduced inflammation in mice ears and legs. Leg and ear inflammation decreased by 10-60% and 50-60%, respectively, in comparison to control. Phenolic chemicals, terpenes and saponins are thought to be responsible for the anti-inflammatory effects seen in these investigations. The primary way in which these chemicals suppress inflammatory processes is by inhibiting regulating enzymes, including phospholipases (PLs), lipoxygenases (LOXs) and cyclooxygenases (COXs). These enzymes have a significant impact on the release of arachidonic acid, a precursor to the manufacture of eicosanoids like prostacyclin and prostaglandins that are closely linked to the inflammatory response. These bioactive substances also inhibited protein tyrosine kinases (PTKs), protein kinase C(PKC) and phosphodiesterase (PDE), which are other regulatory enzymes implicated in inflammation and the immunological response.

Furthermore, terpenes, saponins and phenolic compounds are linked to the suppression of other significant elements involved in the inflammatory process, such as transcriptional factors, nitric oxide (NO), tumor necrosis factor-alpha (TNF-α) and interleukin (IL). These substances often work by inhibiting histamine release, prostanoid production, protein kinases (PKs) and transcription activation to reduce inflammation (Lopez *et al.,* 2018). Additionally, the anthelmintic properties of the 100 mg/kg aqueous extract of *A. salmiana* leaf considerably reduce the quantity of *Heterakis gallinarum* worms and their egg counts. In gastric ulcers caused by ethanol and indomethacin, hecogenin, a steroid saponin that was extracted from *A. salmiana* leaves, showed antiulcer qualities. Hecogenin's gastroprotective action relied on K-ATP channels (Herrera *et al.,* 2022).

4.3 Antihepatotoxic properties

The hepatotoxicity that paracetamol induces can be avoided with *A. americana* extract. In the liver, paracetamol causes fibrosis, mononuclear cell infiltration, steatosis and hepatocyte disintegration, all of which are histological changes suggestive of liver damage. It also causes necrosis and apoptosis. Flavonoids and phenolics have a broad range of biological and pharmacological effects because they are essential in lowering oxidative stress and scavenging free radicals. Through the prevention of molecular changes, oxidative stress and toxic chemical reactions in the liver tissues that ultimately lead to necrosis. Pretreatment with *A. americana* extract protects the liver tissue and hepatic architecture from prominent foci of mononuclear infiltration of hepatic parenchyma tissue, sinusoid and around the central vein, as well as from tissue disorder and necrosis (Ayenew and Wasihun, 2023).

4.4 Antidiabetic properties

Diabetes mellitus is a chronic metabolic condition that causes loss of glucose homeostasis due to a deficiency in insulin production or activity. In India, this serious endocrine condition is quickly becoming a possible epidemic. Hyperglycemia, elevated free fatty acids, insulin resistance, and other metabolic abnormalities that define diabetes can trigger molecular processes that lead to vascular dysfunction. Diabetes raises the risk of heart disease, stroke, and microvascular consequences such as peripheral neuropathy, blindness, and kidney failure, making it a serious health issue (Shahul *et al.,* 2018). The *A. lechuguilla* Torr., often referred to as lechuguilla locally, is empirically harvested by residents of dry and semi-arid regions of Mexico as a common pool resource for its fiber. Guishe is a useless vegetable pulp that is left over after fiber extraction from bagasse. It is a plentiful and underappreciated plant material that contains flavonoids and other naturally occurring active chemicals. The phytochemicals found in lechuguilla crude extracts, particularly some anthocyanins like cyanidin and hesperidin, have positive effects on diabetes mellitus and a few other illnesses. In diabetic rats, both types of molecules have demonstrated antidiabetic and hypolipidemic effects by increasing glucose uptake in primary adipocytes and phosphorylating the insulin receptor in the liver, respectively. Furthermore, it has been demonstrated that a significant amount of saponins is present in guishe aqueous extracts. It is well known that saponins have antidiabetic effects (Esquivel *et al.,* 2021).

4.5 Antiarthritic properties

A steroidal sapogenin called hecogenin was extracted from the leaves of several *Agave* species, including *A. cantala, A. sisalana and A. aurea*. Hecogenin's antiarthritic properties were demonstrated by Ingawale and Patel (2018) in rats with arthritis produced by full Freund's adjuvant by suppressing proinflammatory cytokines. According to the study, hecogenin significantly decreased paw edema, arthritic score and joint diameter while also preventing joint degradation in ankle joint histological and radiological analyses. Following hecogenin treatment, it was discovered that the biochemical levels of serum transaminase, serum phosphatase, myeloperoxidase and inflammatory cytokines like interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), thromboxane B2 (TXB2), and interleukin-12 (IL-12), as well as haematological parameters like hemoglobin and blood cells, had decreased. COX-2 mRNA expression and histopathology of rats confirmed the antiarthritic efficacy. A histopathological study revealed that the hecogenin-treated ankle joint significantly inhibited soft tissue swelling, bone degradation and joint space narrowing. Rats treated with hecogenin showed decreased levels of COX-2 mRNA enzymes which shows the anti-arthritic properties of hecogenin (Ingawale and Patel, 2018).

4.6 Antihypertensive properties

A. americana extracts revealed antihypertensive action using the angiotensin-converting enzyme (ACE) test, with 25 μg attaining 72% (aqueous extract) and 82% (ethanol extract) ACE inhibition, revealing their potential for alleviating high blood pressure. The presence of phenolic chemicals, terpenes and saponins is most likely the main factor influencing the antihypertensive action of *Agave* extracts. Antioxidant activity against reactive oxygen species (ROS) generation, which is linked to the development of cardiovascular disease, produces antihypertensive effects (Lopez *et al.,* 2018). For instance, several investigations have shown that these substances reduced or blocked the generation of ROS, including ONOO-and O2-which are implicated in hypertension (Shouk *et al.,* 2014). The primary source of O2- in endothelial cells, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase is inhibited which is the reason for these effects. These substances also have significant antihypertensive effects on the kidneys, which are linked to a reduction in blood pressure through the downregulation of the kidney's epithelial sodium channel (ENaC). This substance may also suppress the expression of matrix metalloproteinases, protein kinases and inflammatory molecules linked to cell growth and apoptosis, which may disrupt blood pressure regulation (Perez *et al.,* 2009).

4.7 Antiparasitic properties

Leishmania donovani, the cause of visceral leishmaniasis, is susceptible to the antiparasitic effects of *Agave*. Amastigotes and promastigotes of *L. donovani* were killed by *A. americana* leaf extracts at 0.05 mg/l; however, this impact was best seen on amastigotes that had 100% mortality. Analogously to the commercial medication amphotericin B, which is frequently utilized to treat visceral leishmaniasis, the toxicity of extract to this medicine was comparable. However, the high expense of treatment is a restriction. *A. americana* leaf extracts which are fractionated using ethyl-acetate demonstrated 100% mortality at 50 g/ml against *L. donovani*. The potential mechanism of action of extract was proposed to be that the application of effective doses enhances the levels of nitric oxide in macrophages afflicted with amastigotes (Bermudez *et al.,* 2021). Nevertheless, the hemolytic effect and cytotoxicity on macrophages were visible at 48h after dosage. *A. lechuguilla Torr*. exhibited 69.66% growth inhibition towards *Entamoeba hystolytica*, the amoebiasis-causing agent, proving its antiparasitic potential; however, no median fatal dose was identified.

Trichomonas vaginalis, Entamoeba histolytica and *Giardia lamblia are* inhibited by the extract of *A. lophantha*. At 10 µg/ml, 100 µg/ml and 500 µg/ml, *A. brittoniana* also has antiparasitic efficacy against *Trichomonas vaginalis*. Phenolic chemicals, terpenes and saponins, which have distinct mechanisms of action, provide antiparasitic properties to *Agave* extracts. Saponins are mostly linked to pore development and changes in membrane permeability, although the precise process is unknown. Since saponins are lipophilic, they can interact with biomembranes and alter the fluidity and function of membrane proteins, which gives antiparasitic properties to the particular extract with saponin. The action of these molecules is determined by the quantity and type of sugar moieties as these characteristics affect the hydrophobicity of a molecule. The action of these molecules is determined by the quantity and type of sugar moieties as these characteristics affect the hydrophobicity of a molecule. As with saponins, terpenes can disrupt membranes; this effect was linked to the hydrophobic properties of these substances. In parasites, terpenes promote lipid oxidation, which leads to the formation of excess reactive oxygen species (ROS) that may harm mitochondria. These substances also cause irreversible DNA damage and block essential enzymes like topoisomerase reductase (Lopez *et al.,* 2018). Another class of compounds found in *Agave* extracts that have antiparasitic properties are flavonoids. They can cause changes in the membrane of parasites. Flavonoids having a double bond in both the B ring and the C ring connected to C-2 are more effective against parasites. Flavonoids have a significant influence on the suppression of enzymes that facilitate invasion, differentiation and proliferation. Furthermore, these substances influence DNA replication by inhibiting topoisomerase I and II, which destroy parasites.

4.8 Immunomodulatory effects

Leaves of *A. marmorata* have immunomodulatory effects. It is due to the presence of smilagenin-diglycoside. Compounds like octadecadienoic acid-2,3-dihydroxypropyl ester, β-sitosterol glycoside, phytol, cycloartenone, cycloartenol and stigmasta-3,5-dien-7-one, present in *A. tequilana* stem and 3-O-[(6 -O-palmitoyl)-β-D-glucopiranosyl-sitosterol] in *A. angustifolia* leaves possess immunomodulatory effect at the dosage of 50 mg/kg (Gutierrez *et al.,* 2017; Hernandez *et al.,* 2014). *A. seemanniana* leaves have analgesic, anti-inflammatory and antiulcerogenic properties which is because of the presence of steroidal saponins. The fresh leaves of the *A. applanata,* are used to make an ethanol tonic that lowers blood sugar levels. When compared to the ranitidine (20 mg/kg) group, treatment with *Agave* extracts dramatically decreased the quantity and intensity of ethanol-induced stomach lesions. Comparable to ranitidine, *A. angustifolia* var. *marginata* had a strong ulcer-protective effect, reducing ulcer number and severity by roughly 84% and 91%, respectively. In a similar vein, *A. pygmaea* caused an approximate 81% and 85% reduction in the quantity and severity of alcohol-induced ulcers (El-Dine, 2023). Additionally, it can be applied directly to treat wounds, inflammation and infections associated with diabetic foot ulcers and varicose ulcers (Aguilar *et al.,* 2024).

5. *Agave* syrup and its importance

The culinary product known as *Agave* syrup or *Agave* nectar is manufactured from the sap of *Agave*, specifically *A. salmiana* (salmiana) and *A. tequilana* (blue agave). This product has gained popularity as a vegan alternative to conventional sweeteners like honey and table sugar (sucrose) due to its low glycemic index. The first step in producing *Agave* syrup is harvesting mature *Agave* plants that are 5-7 years old. Among them, pinas (pine) with high amounts of carbohydrates can be stored. After removing the leaves, a pine resembles a pineapple (Castro *et al.,* 2022). To acquire juicy fibers, the next step is to crush and grind the pinas. After removing the fibers and washing them in hot water in a diffuser, raw *Agave* juices are filtered to remove any remaining solid particle residue. Before being refiltered, the filtered juice should hydrolyze thermally by heating it to 80°C for 8 to 12 h. The water content is reduced by a second filtration. The juice is then evaporated at 90°C in a vacuum to modify the glycosidic activity. Thus, the final syrup product is produced (Maldonado *et al.,* 2018).

Agavins are a distinct molecule found in *Agave* plants. They are reserve carbohydrates made up of one special glucose and fructose polymer. They are considered prebiotic materials with a variety of uses like working as wall material and encapsulating bioactive chemicals. Because of their unique molecular and phytochemical makeup, agavins are not broken down by digestive enzymes in the small intestine or by the oral microbiota in the mouth. However, when agavins reach the large intestine, the intestinal microbiota ferments them, which encourages the growth of the primary probiotics, *Lactobacillus* sp., *Saccharomyces boulardii* and *Bifidobacterium* sp.. When mice are fed *Agave* syrup, their body weight loss is accelerated due to microbiota alteration and the presence of short-chain fatty acids (Huazano *et al.,* 2017). Agavins, which are classified as prebiotics, are known to benefit the host's health by altering the activity and/or composition of the intestinal microbiota. This action on the microbiome is due to their structural complexity. When agavins go through the stomach and small intestine, they are not broken down by the natural digestive enzymes of the body. They reach the colon and caecum. Here, they are fermented by the saccharolytic microbiotas found in these locations to create short-chain fatty acids, primarily propionate, acetate and butyrate. Short-chain fatty acids have a significant role in decreasing weight gain, which is shown in Figure 2 through G-protein coupled receptors.

This affects the hormones secreted that are involved in appetite regulation. Due to a reduced pH, agavin fermentation in the gut and caecum can alter the intestinal microbes (Chung *et al.,* 2016). Consumption of organic blue *Agave* syrup from *A. tequilana* at the dosage of 1 g/day for 8 weeks shows a positive effect on glycemia, insulinemia, triglycerides and cholesterol levels.

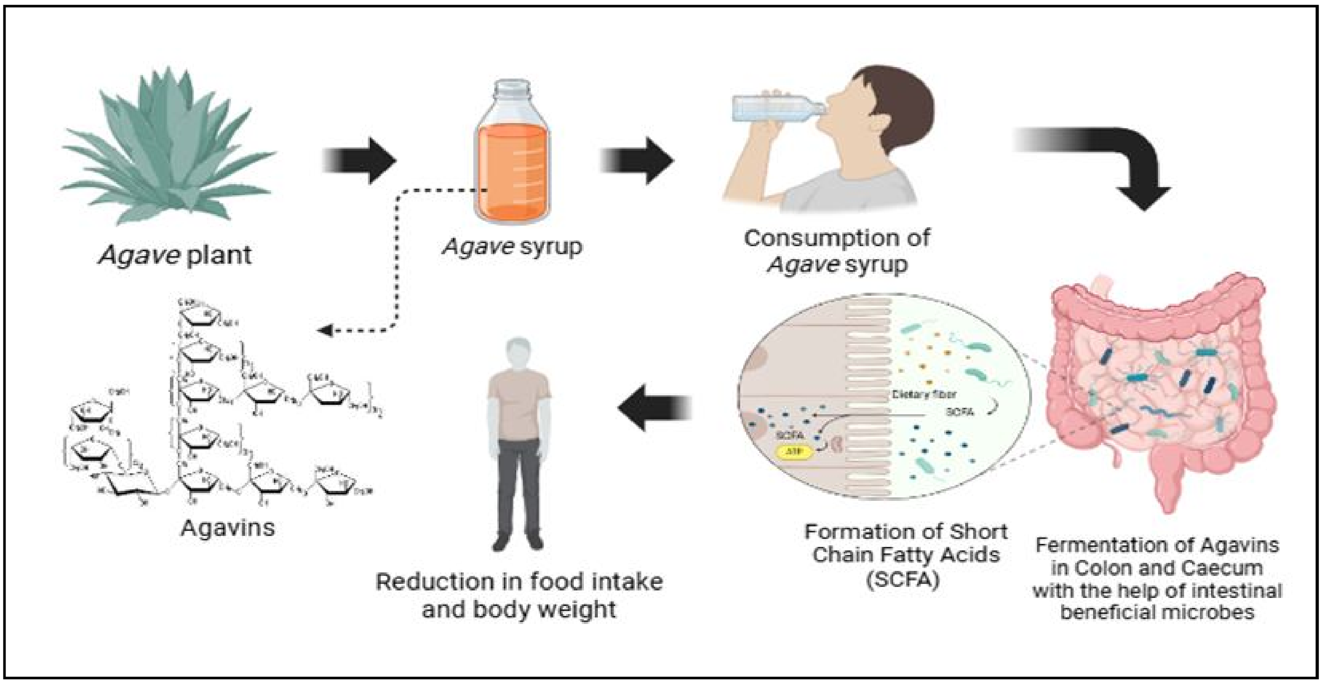

Figure 2 : Mechanism by which consumption of agavins can reduce the food intake and body weight.

6. Antimicrobial properties of *Agave*

According to multiple research studies, *A. sisalana* extracts suppress microbes like *Staphylococcus aureus, Pseudomonas aeruginosa, Escherichia coli and Salmonella typhi*. The components found in the extracts, including tannins, flavonoids, terpenoids, glycosides and saponins, are responsible for this impact. According to many research studies, phenolic chemicals, terpenes and saponins modify the hydrophobicity, surface charge and membrane integrity of bacteria. These modifications cause intracellular contents to seep out, which leads to bacterial cellular death (Borges *et al.,* 2013). Furthermore, according to other research, these bioactive substances exhibited a variety of modes of action, including the inhibition of cytoplasmic membrane functions, the inhibition of energy metabolism, the inhibition of essential enzymes and the inhibition of nucleic acid synthesis which have the potential to cause bacterial death (Thirumurugan *et al.,* 2010). The antibacterial action of saponins, phenolic compounds and terpenes is determined by their structure, molecular size and hydrophobicity. These properties make the chemicals stable and water soluble and make it easier for them to interact with proteins and lipids in membranes. Furthermore, low molecular weight compounds can penetrate the bacterial membrane more easily than higher molecular weight compounds, increasing their interactions with intracellular components and improving their antibacterial properties.

Certain *Agave* species, including *A. americana, A. scabra, A. sisalana, A. angustifolia, A. montana and A. lechuguilla*, showed antisporulant effects or inhibited the growth of mycelial hyphal formation against a variety of fungal species, including *Alternaria brassicae*, *Phytophthora cinnamomi*, *Penicillium digitatum*, *Fussarum oxysporum*, *Pythium aphanidermatum, Sclerotium rolfsii, etc*. The components such as phenolic chemicals, terpenes and saponins of *Agave* extracts are responsible for their antifungal properties. Castillo *et al.* (2015) found that lanolin extract from *A. lechuguilla* species has antifungal action against *Phytophthora cinnamomi*, with an IC_{50} of 23.07 mg/ml. Strong antifungal effects have been shown by phenolic substances such as flavonoids, phenylpropanoids and polyphenols by disruption of the cell membrane, suppression of mitochondrial activity and inhibition of cell wall production. Additionally, these substances can halt cell cycle activities at the S-phase, which prevents cell division and in turn, impacts the proliferation of fungal cells (Davidson *et al.,* 2012). On the other hand, antifungal processes of terpenes are mostly linked to the breakdown of cell walls and membranes, the suppression of electron flow, proton motive force, active transport and essential enzymes, as well as the coagulation of cell contents, which causes intracellular components to seep out. The polarity of terpenes is linked to their antifungal action because less polar molecules readily interact with membrane lipid components, altering their permeability and enabling fungal death.

7. Antioxidant properties of *Agave*

Antioxidants protect lipids, proteins, enzymes, carbohydrates, and DNA from being damaged and significantly mitigate the harm that free radicals do before they assault cells. When the equilibrium between reactive oxygen species and the antioxidant system is destroyed, oxidative stress can occur, which is a major factor in the development and progression of several illnesses. The Indian alternative medical systems have been using herbal antioxidants as rejuvenators for many generations (Manju and Pushpa, 2020). *Agave* extracts have high antioxidant potential due to the presence of phenolic components like flavonoids. Because of the chromane and catechol groups included in their structures, these compounds exhibit a high level of antioxidant activity. Terpenes and flavonoids both possess antioxidant potential; however, the presence of hydroxyl groups, conjugated systems, phenolic structure and numerous bonds are some of the structural features that affect their antioxidant activity. Hamissa *et al.* (2012) discovered polyphenols and flavonoids in *A. americana* extracts, which have antioxidant properties. Using a reducing power assay, the scientists found a positive association between the phenolic compounds ($R^2 = 0.94$) and antioxidant activity, which led them to attribute the antioxidant effect to the extracts. The concentrated sap of *A. mapisaga* has good antioxidant capacity. Phenolic chemicals and terpenes have significant antioxidant activity; saponins are known to have less of it. Hydroxyl groups and oligosaccharide moieties at C-3 contribute significantly to the antioxidant properties, as well as their ability to give hydrogen atoms or electrons to stop radical chain reactions (Xiong *et al.,* 2012).

8. Conclusion

Agave species are a vital asset in modern medicine owing to their broad array of bioactive chemicals, which can treat a wide range of ailments. Due to its immunomodulatory, anti-inflammatory, antibacterial, antioxidant, anticancer properties, *etc*. *Agave* has been used in traditional medicine since ancient times. The diverse chemical makeup of *Agave* which contains terpenes, steroids, flavonoids and saponins, enables a variety of biological actions that can be harnessed medicinally. Recent studies have highlighted significant pharmacological benefits of *Agave*, particularly its ability to lower oxidative stress, its promise as an anticancer drug and its effectiveness against bacterial and fungal infections. *Agave* extract can also prevent cellular damage and lower inflammation. Despite these beneficial results, additional research is necessary to fully comprehend the mechanisms underlying the therapeutic properties, refine extraction and formulation methodologies and evaluate its reliability and efficacy in clinical settings. *Agave* is a unique botanical that has a lot of potential to support or even enhance modern medical treatments, particularly as interest in plant-based remedies continues to rise. Given its immense potential in pharmacology, nutrition, sustainable agriculture and cosmetics *Agave* seems to have a bright future in modern healthcare. It will take thorough clinical studies, continued research into its bioactive compounds and advancements in extraction methods to fully realize the therapeutic properties of this versatile plant. In conclusion, *Agave* is a vast supplier of medicinal compounds with an array of applications in medicine, pharmacology and nutrition. *Agave* could have a significant role in natural and integrative healthcare therapies in the future if its bioactive ingredients and therapeutic qualities are further analyzed.

Conflict of interest

The authors declare no conflicts of interest relevant to this article.

References

Aguilar Guadarrama, A. B.; Diaz Roman, M. A.; Osorio Garcia, M.; Deciga Campos, M. and Rios, M. Y. (2024). Chemical constituents from *Agave applanata* and its antihyperglycemic, anti-inflammatory and antimicrobial activities associated with its tissue repair capability. Planta Medica, **90**(05):397-410.

Ahumada Santos, Y. P.; Montes Avila, J.; de Jesús Uribe Beltran, M.; Diaz Camacho, S. P.; Lopez Angulo, G.; Vega Avina, R. and Delgado Vargas, F. (2013). Chemical characterization, antioxidant and antibacterial activities of six *Agave* species from Sinaloa, Mexico. Industrial Crops and Products, **4**: 143-149.

Alvarez Garcia, P.; Alcantara Quintana, L. E.; Ruiz Cabrera, M. A.; Martinez Gutierrez, F.; Gonzalez Garcia, R. and Grajales Lagunes, A. (2023). Fructan mixtures of *Agave salmiana* and chicory exhibit *in vitro* anticancer potential in human colon cells and prebiotic activity. Cogent Food and Agriculture, **9**(1):2196871.

Anajwala, C. C.; Patel, R. M.; Dakhara, S. L. and Jariwala, J. K. (2010). *In vitro* cytotoxicity study of *Agave americana* , *Strychnos nuxvomica* and *Areca catechu* extracts using MCF-7 cell line. Journal of Advanced Pharmaceutical Technology and Research, **1**(2):245-252.

Ayenew, K. D. and Wasihun, Y. (2023). Hepatoprotective effect of methanol extract of *Agave americana* leaves on paracetamol induced hepatotoxicity in Wistar albino rats. BMC Complementary Medicine and Therapies, **23**(1):99.

Babu, M. P.; Dang, R. and Das, K. (2015). Phytochemical investigations and characterization of antimicrobial activity of bioguided fractionated leaves of *Agave americana*. Ann. Phytomed., **4**(1):61-67.

Bermudez Bazan, M.; Castillo Herrera, G. A.; Urias Silvas, J. E.; Escobedo Reyes, A. and Estarron Espinosa, M. (2021). Hunting bioactive molecules from the *Agave* genus: An update on extraction and biological potential. Molecules, **26**(22): 6789.

Bhalla, Y.; Gupta, V. K. and Jaitak, V. (2013). Anticancer activity of essential oils: a review. Journal of the Science of Food and Agriculture, **93**(15): 3643-3653.

Borges, A.; Ferreira, C.; Saavedra, M. J. and Simoes, M. (2013). Antibacterial activity and mode of action of ferulic and gallic acids against pathogenic bacteria. Microbial Drug Resistance, **19**(4):256-265.

Bouaziz, M. A.; Rassaoui, R. and Besbes, S. (2014). Chemical composition, functional properties and effect of inulin from Tunisian *Agave americana* L. leaves on textural qualities of pectin gel. Journal of Chemistry, **2014**(1): 758697.

Brackenbury, T. D. and Appleton, C. C. (1997). A comprehensive evaluation of *Agave attenuata*, a candidate plant molluscicide in South Africa. Acta Tropica, **68**(2):201-213.

Castillo Reyes, F.; Clemente Constantino, J. A.; Gallegos Morales, G.; RodrAguez Herrera, R. and NoA, C. (2015). *In vitro* antifungal activity of polyphenols-rich plant extracts against *Phytophthora cinnamomi* Rands. African Journal of Agricultural Research, **10**(50):4554-4560.

Castro Munoz, R.; Correa Delgado, M.; Cordova Almeida, R.; Lara Nava, D.; Chavez Munoz, M.; Velasquez Chavez, V. F. and Ahmad, M. Z. (2022). Natural sweeteners: Sources, extraction and current uses in foods and food industries. Food Chemistry, **370**:130991.

Chaachouay, N.; Benkhnigue, O. and Zidane, L. (2020). Ethnobotanical study aimed at investigating the use of medicinal plants to treat nervous system diseases in the Rif of Morocco. Journal of Chiropractic Medicine, **19**(1):70-81.

Cheruku; Sandeep and Shaheedha, S.M. (2024). Unveiling cytotoxic potential of herbal extracts: *Plectronia parviflora* and *Agave cantula* against MCF and HCT cell Lines. International Journal of Pharmaceutical Quality Assurance. **15**:135-140.

Chikara, P.; Deep, A.; Bansal, N.; Kumar, S.; Bansal, S.; Sharma, A. K. and Marwaha, R. K. (2023). Phytochemical screening and biological potential of *Agave angustifolia* Haw. leaves extract as antioxidant and anticancer agents. Current Cancer Therapy Reviews, **19**(1):58-66.

Chung, W. S. F.; Walker, A. W.; Louis, P.; Parkhill, J.; Vermeiren, J.; Bosscher, D. and Flint, H. J. (2016). Modulation of the human gut microbiota by dietary fibres occurs at the species level. BMC biology, **14**:1-13.

Davidson, P. M.; Taylor, T. M. and Schmidt, S. E. (2012). Chemical preservatives and natural antimicrobial compounds. Food microbiology: Fundamentals and Frontiers, pp:765-801.

Davis, S. C. (2022). *Agave americana* : Characteristics and potential breeding priorities. Plants, **11**(17):2305.

Debnath, M.; Pandey, M.; Sharma, R.; Thakur, G. S. and Lal, P. (2010). Biotechnological intervention of *Agave sisalana*: A unique fiber yielding plant with medicinal property. Journal of Medicinal Plants Research, **4**(3):177-187.

Dehghan, P.; Gargari, B. P.; Jafar Abadi, M. A. and Aliasgharzadeh, A. (2014). Inulin controls inflammation and metabolic endotoxemia in women with type 2 diabetes mellitus: A randomized-controlled clinical trial. International Journal of Food Sciences and Nutrition, **65**(1): 117-123.

Delgado Lemus, A.; Casas, A.; and Tellez, O. (2014). Distribution, abundance and traditional management of *Agave potatorum* in the Tehuacan Valley, Mexico: Bases for sustainable use of non-timber forest products. Journal of Ethnobiology and Ethnomedicine, **10**:1-12.

Depommier, C.; Everard, A.; Druart, C.; Plovier, H.; Van Hul, M.; Vieira Silva, S. and Cani, P. D. (2019). Supplementation with *Akkermansia muciniphila* in overweight and obese human volunteers: A proof-of-concept exploratory study. Nature Medicine, **25**(7):1096-1103.

Dunder, R. J.; Quaglio, A. E.; Maciel, R. P.; Luiz Ferreira, A.; Almeida, A. C.; Takayama, C. and Souza Brito, A. R. (2010). Anti-inflammatory and analgesic potential of hydrolyzed extract of *Agave sisalana* Perrine ex Engelm.; Asparagaceae. Revista Brasileira de Farmacognosia, **20**: 376-381.

El Dine, S. (2023) Metabolomic profiling of five *Agave* leaf taxa *via* UHPLC/PDA/ESI-MS in relation to their anti-inflammatory, immunomodulatory and ulceroprotective activities. Reviews: pp:419.

El Hawary, S. S.; El Kammar, H. A.; Farag, M. A.; Saleh, D. O. and El Dine, saR. S. (2020). Metabolomic profiling of five *Agave* leaf taxa *via* UHPLC/PDA/ESI-MS inrelation to their anti-inflammatory, immunomodulatory and ulceroprotective activities. Steroids, **160**:108648.

El Hilaly, J.; Hmammouchi, M. and Lyoussi, B. (2003). Ethnobotanical studies and economic evaluation of medicinal plants in Taounate province (Northern Morocco). Journal of Ethnopharmacology, **86**(2-3): 149-158.

Espinosa Andrews, H.; Urias Silvas, J. E. and Morales Hernandez, N. (2021). The role of *Agave* fructans in health and food applications: A review. Trends in Food Science and Technology, **114**:585-598.

Esquivel Gutierrez, E. R.; Manzo Avalos, S.; Pena Montes, D. J.; Saavedra Molina, A.; Morreeuw, Z. P. and Reyes, A. G. (2021). Hypolipidemic and antioxidant effects of Guishe extract from *Agave lechuguilla*, a Mexican plant with biotechnological potential, on streptozotocin-induced diabetic male rats. Plants, **10**(11):2492.

Greay, S. J. and Hammer, K. A. (2015). Recent developments in the bioactivity of mono-and diterpenes: Anticancer and antimicrobial activity. Phytochemistry Reviews, **14**:1-6.

Gutierrez Nava, Z. J.; Jimenez Aparicio, A. R.; Herrera Ruiz, M. L. and Jimenez Ferrer, E. (2017). Immunomodulatory effect of *Agave tequilana* evaluated on an autoimmunity like-SLE model induced in Balb/c mice with pristane. Molecules, **22**(6):848.

Hamissa, A. M. B.; Seffen, M.; Aliakbarian, B.; Casazza, A. A.; Perego, P. and Converti, A. (2012). Phenolics extraction from *Agave americana* (L.) leaves using high-temperature, high-pressure reactor. Food and Bioproducts Processing, **90**(1):17-21.

Hernandez Valle, E.; Herrera Ruiz, M.; Rosas Salgado, G.; Zamilpa, A.; Arenas Ocampo, M. L.; Jimenez Aparicio, A. and Jimenez Ferrer, E. (2014). Anti-inflammatory effect of 3-O-[(6'-O-palmitoyl)-â-D-glucopyranosyl sitosterol] from *Agave angustifolia* on ear edema in mice. Molecules, **19**(10):15624-15637.

Herrera Ruiz, M.; Jimenez Ferrer, E.; Gonzalez Cortazar, M.; Zamilpa, A.; Cardoso Taketa, A.; Arenas Ocampo, M. L. and Monterrosas Brisson, N. (2022). Potential use of *Agave* genus in neuroinflammation management. Plants, **11**(17):2208.

Huazano Garcia, A.; Shin, H. and Lopez, M. G. (2017). Modulation of gut microbiota of overweight mice by agavins and their association with body weight loss. Nutrients, **9**(9):821.

Ingawale, D. K. (2020). Saponins and sapogenins of *Agave* with respect to diverse pharmacological role of hecogenin. Int. J. Pharm. Pharm. Sci., **12**(2): 1-7.

Ingawale, D. K. and Patel, S. S. (2018). Hecogenin exhibits anti-arthritic activity in rats through suppression of pro-inflammatory cytokines in complete Freund's adjuvant-induced arthritis. Immunopharmacology and Immunotoxicology, **40**(1):59-71.

Kablan, R. J. F.; Sylvestre, M.; Onesippe Potiron, C.; Bilba, K., Kablan, A. L. C.; Arsene, M. A. and Cebrian Torrejon, G. (2024). Agave species: A comprehensive review of taxonomy, chemistry, ethnobotany and ethnopharmacology. Studies in Natural Products Chemistry, **80**: 187-225.

Lopez Romero, J. C.; Ayala Zavala, J. F.; Gonzalez Aguilar, G. A.; Pena Ramos, E. A. and Gonzalez Rios, H. (2018). Biological activities of *Agave* by products and their possible applications in food and pharmaceuticals. Journal of the Science of Food and Agriculture, **98**(7):2461-2474.

Maldonado Guevara, B. I.; Martin del Campo, S. T. and Cardador Martinez, A. (2018). Production process effect on Mexican *Agave* syrups quality: a preliminary study. Reviews, **7**:50-57.

Manju, P. and Pushpa, A. (2020). Phytochemical analysis and *in vitro* free radical scavenging activity of rhizome of *Zingiber officinale* Rosc. Ann. Phytomed., **9**(2):257-262.

Marquez Rangel, I.; Cruz, M.; Ruiz, H. A.; Rodriguez Jasso; R. M., Loredo, A. and Belmares, R. (2023). *Agave* waste as a source of prebiotic polymers: Technological applications in food and their beneficial health effect. Food Bioscience, 103102.

Peana, A. T.; Moretti, M. D.; Manconi, V.; Desole, G. and Pippia, P. (1997). Anti-inflammatory activity of aqueous extracts and steroidal sapogenins of *Agave americana*. Planta Medica, **63**(03):199-202.

Pereira, G. M.; Ribeiro, M. G.; da Silva, B. P. and Parente, J. P. (2017). Structural characterization of a new steroidal saponin from *Agave angustifolia* var. *Marginata* and a preliminary investigation of its *in vivo* antiulcerogenic activity and *in vitro* membrane permeability property. Bioorganic and Medicinal Chemistry Letters, **27**(18): 4345-4349.

Perez Vizcaino, F.; Duarte, J.; Jimenez, R.; Santos Buelga, C. and Osuna, A. (2009). Antihypertensive effects of the flavonoid quercetin. Pharmacological Reports, **61**(1):67-75.

Perez Zavala, M. D. L.; Hernandez Arzaba, J. C.; Bideshi, D. K. and Barboza Corona, J. E. (2020). *Agave*: A natural renewable resource with multiple applications. Journal of the Science of Food and Agriculture, **100**(15): 5324-5333.

Sahnoun, M.; Bejar, S.; Daoud, L.; Ayadi, L.; Brini, F. and Saibi, W. (2019). Effect of *Agave americana* L. on the human and *Aspergillus oryzae* S2 α-amylase inhibitions. Natural product research, **33**(5): 755-758.

Santiago Martinez, A.; Perez Herrera, A.; Martinez Gutierrez, G. A. and Meneses, M. E. (2023). Contributions of *Agave*s to human health and nutrition. Food Bioscience, **53**:102753.

Santos Zea, L.; Fajardo Ramirez, O. R.; Romo Lopez, I. and Gutierrez Uribe, J. A. (2016). Fast centrifugal partition chromatography fractionation of concentrated *Agave* (*Agave salmiana*) sap to obtain saponins with apoptotic effect on colon cancer cells. Plant Foods for Human Nutrition, **71**:57-63.

Santos Zea, L.; Maria Leal Diaz, A.; Cortes Ceballos, E. and Alejandra Gutierrez Uribe, J. (2012). Agave (*Agave* spp.) and its traditional products as a source of bioactive compounds. Current Bioactive Compounds, **8**(3):218-231.

Shaul Ahmed, R.; Patel, U. D.; Bhadarka, D. H.; Patel, H. B. and Modi, C. M. (2018). Modulation of antioxidant defense system by polyherbal extract mixture which ameliorated the pathophysiological alterations in streptozotocin induced diabetic rats. Ann Phytomed., **7**(2): 102-113.

Sheikh Raisuddin, S. A.; Fatima, M. and Dabeer, S. (2018). Toxicity of anticancer drugs and its prevention with special reference to role of garlic constituents. Ann. Phytomed., **7**(1):13-26.

Shouk, R.; Abdou, A.; Shetty, K.; Sarkar, D. and Eid, A. H. (2014). Mechanisms underlying the antihypertensive effects of garlic bioactives. Nutrition Research, **34**(2):106-115.

Sidana, J.; Singh, B. and Sharma, O. P. (2016). Saponins of *Agave*: Chemistry and bioactivity. Phytochemistry, **130**: 22-46.

Thirumurugan, K.; Shihabudeen, M. S. and Hansi, P. D. (2010). Antimicrobial activity and phytochemical analysis of selected Indian folk medicinal plants. Steroids, **1**(7):430-434.

Torre, L. D. L.; Cummins, I. and Logan Hines, E. (2018). *Agave americana* and *Furcraea andina*: Key species to Andean cultures in Ecuador. Botanical Sciences, **96**(2):246-266.

Xiong, S. L.; Hou, D. B.; Huang, N. and Li, A. (2012). Preparation and biological activity of saponin from *Ophiopogon japonicus*. African Journal of Pharmacy and Pharmacology, **6**(26):1964-1970.

Zhou, K. (2017). Strategies to promote abundance of *Akkermansia muciniphila*, an emerging probiotics in the gut, evidence from dietary intervention studies. Journal of functional foods, **33**:194-201.

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