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Review

Botanical, genetic, phytochemical and pharmaceutical aspects of *Annona cherimola* Mill

Anna Perrone [a], Sanaz Yousefi [b], Alireza Salami [c], Alessio Papini [d], Federico Martinelli [d,*]

[a] Department of Biological, Chemical and Pharmaceutical Sciences and Technologies (STEBICEF), University of Palermo, Viale delle Scienze, Palermo, 90128, Italy
[b] Department of Horticultural Science, Bu-Ali Sina University, Hamedan, Iran
[c] Department of Horticultural Sciences, Faculty of Agriculture and Natural Resources, University of Teheran, Iran
[d] Department of Biology, University of Florence, Sesto Fiorentino, Florence, 50019, Italy

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ABSTRACT

The cherimoya (*Annona cherimola*), also named chirimoya, is an edible fruit tree of the genus Annona belonging to the family Annonaceae. It is mostly present in tropical and subtropical world regions. This plant species has a long history of use in folk traditional medicine against degenerative and chronic diseases. Fruit and leaf tissues are used as beverages, infusions, fruit, marmalades, and other traditional processed foods. A great extent of different flavors, textures, and shapes are available in food products derived from this plant. Several research works have identified the phytochemicals and bioactive compounds that can be extracted from the plant organs, verifying their antioxidant, anti-degenerative disease, anti-cancer, anti-chronic diseases, and anti-microbial properties. Acetogenins, polyphenols, and terpenes are important components of *A. cherimola* Mill. Although they are widely present in different plant organs, different classes of compounds showed to accumulate more in seeds (polyphenols), leaves (terpenes), and both leaves and fruits (acetogenins) of chirimoya. In this comprehensive review, evidences have been provided about the healthy and beneficial activities of the plant, briefly explaining the results of previous research works in this regard. Information regarding phytochemistry, traditional uses, and biological activities of chirimoya is also provided here. We believe to have provided a unique resource that collects and discusses scientific evidences at the pharmaceutical and health level for providing the ground for the development of treatment formulations against serious and highly threatening diseases. The collected results will be helpful also as a basis for further investigations on single specific Annona compounds.

1. Introduction

The therapeutic potential of food has been already suggested two thousand years ago by Hippocrates, the father of modern medicine, with the aphorism "Let food be your medicine and medicine be your food". The importance of food for the maintenance of health and even healing of illness is now widely demonstrated by numerous scientific evidence (Agarwal and Rao, 2000; Lampe, 1999; Ronco et al., 1999) so that nowadays the concept is often investigated as a new independent field named "nutraceutics". The modern consumer, in the increasingly deep-rooted belief of the active role that nutrition can have on his state of health, is increasingly getting careful in choosing high-quality foods. The consumption of food does not depend anymore on good looks, taste, and smells, but also on its potential health value.

The term "nutraceutical", used for the first time as a fusion of the terms "nutrition" and "drug", refers to "single components" or fractions of food with proven beneficial effects on health, formulated and administered, like drugs, in a specific dosage (Kalra, 2003). Therefore, a nutraceutical is a food component that, due to its functional properties, is located precisely at the limit between a food and a drug. The market for functional foods and nutraceuticals, although still "niche", has undergone a rapid increase in recent years. The reasons for this growth are to be found in the growing awareness on the part of the modern consumer about the role of diet in 1) maintaining the state of health and well-being in 2) the increase in pathologies associated with sedentary life and unbalanced diets (obesity, osteoporosis, diabetes, cardiovascular pathologies, cancer, etc.) and in the consequent dizzying increase in health expenditure for healthy food. Nutraceuticals, a term that indicates the specific nutritional field that studies and develops the potential health properties of foods and their components, immediately indicate great

* Corresponding author at: Università degli Studi di Firenze: Universita degli Studi di Firenze, Italy
E-mail address: federico.martinelli@unifi.it (F. Martinelli).

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commercial potential. In fact, the consumer's interest in a potential health value of food stimulates the interest of the producer in the development of this putative beneficial function. Those substances that exert an effect on a living organism, tissue, or cell are called bioactive. The presence of bioactive components in food can give that food potential beneficial effects to preserve health.

2. Phytochemicals and bioactive compounds

Bioactive substances are naturally present in nature or can be synthesized. Plants are the most important source of natural bioactive substances and still represent today the main source for the research of new drugs. The bioactive components derived from plants or phytochemical compounds constitute an extremely diversified set of substances belonging to numerous chemical classes and botanical families, for which some bioactivity has been highlighted. This heterogenous set of molecules has the following four common features: 1) they are compounds characteristic of the plant kingdom and normally not synthesized by animal cells, 2) they are organic compounds with low molecular weight, 3) they are not indispensable metabolites for the organism that synthesizes them (secondary metabolites), 4) they have biological activity and are potentially useful for producing benefits on human health after ingestion in significant quantities (Noratto et al., 2009).

The most abundant and widespread phytochemical compounds belong to the chemical group of polyphenols, a name comprising several classes of molecules (flavonoids, phenolic acids, stilbenes, lignans, and xanthones), including a benzene ring with one or more associated hydroxyl groups (Scalbert and Williamson, 2000). The production of these secondary metabolites plays an important role in the physiology of the plant, for example giving it resistance to microorganisms, insects and favoring pollination (flower coloring) and seed dispersal (aroma, flavor, fruit color). Polyphenols are the most abundant antioxidants in our diet (Ishiwata et al., 2004). Numerous experimental data suggest that these substances are capable of influencing numerous biological processes, modulating the function of several cellular targets (Kaur and Kapoor, 2001).

The biological activity of these molecules is often linked to their reducing and antioxidant properties, referable to their chemical structure that allows these compounds to function as free radical scavengers (Miller and Rice-Evans, 1996) and thus protect the cellular constituents from oxidative damage (Czeczot, 2000). The intake of polyphenols with the diet can thus help to increase the organic antioxidant defenses and can thus positively influence the cellular redox balance, contributing to the prevention of organic oxidative stress phenomena. These last are involved in the etiopathogenesis of numerous pathologies and the physiological phenomenon of aging (Reuter et al., 2010). The biological activity of polyphenols, correlated to their reducing properties, is not only limited to their ability to prevent oxidative stress phenomena but makes them potentially capable of influencing numerous signal transduction pathways (Sang et al., 2005). In fact, polyphenols can influence the cellular redox balance, whose even small variations, regulate the function of numerous biological targets that control cellular functions (Janssen-Heininger et al., 2008). On the other hand, recent data suggest that the bioactivity of some polyphenols is due to their ability to interact directly with proteins or biological membranes (Verstraeten et al., 2015). The growing consumer interest in the health properties of food has completely changed and somehow enriched the meaning of food quality. The health value of food has in fact become increasingly important and today numerous studies have evaluated the nutraceutical properties of foods of plant origin (Gentile et al., 2015). In recent years, there has been a growing interest in characterizing the nutraceutical profile of tropical fruits. The consumption of these agricultural products has significantly increased in recent years, also as a consequence of the recognized nutritional and nutraceutical value of these fruits (Maciel et al., 2011). One of these valuable fruits is *Annona cherimola* Mill.

3. Botanical aspects of *Annona cherimola* Mill

The Annona cherimola is a fruit tree belonging to the Annonaceae family. Considering that it is widely cultivated in the world, the origin of *Annona cherimola* is still under discussion. One hypothesis state that it is originated from the Andes at 700–2400 m of altitude while an alternative hypothesis postulates that Central America is the origin of *Annona cherimola* due to the high presence of wild relatives. The inter-Andean origin would make of *A. cherimola* the only one of the 12 species of the *Atta* section not native to Central America and the Caribbean (Larranaga et al., 2019; Vanhove and Damme, 2013). *Annona cherimola* Mill, is a species belonging to section *Atta* (Fries, 1959). It is the only one of the section native of South America. This species is considered probably native of the territory between Ecuador and Peru. It seems that it was already cultivated in 1200 BCE during the Inca empire. However, more recent investigations based on biogeographical analysis with SSR markers support a probable Mesoamerican origin for *A. cherimola* (Larranaga et al., 2019).

Among Annona species, only *Annona cherimola* Mill is suitable for culturing in subtropical or tropical highland while other species generally are more used for culturing in tropical lowland although their use in subtropics is possible. *A. tripetala* Aiton, *A. pubescens* Salisb are the synonyms for *A. cherimola* Mill, and the most widely recognized names are Cherimolia and Cherimoya. The cherimoya and related species are referred in Central America as Anona. Linnaeus used this word to name the genus Annona. He was alluding to the Latin word Annona which implies the harvest of a year (Linnaeus, 1737). Cherimoya cultivation has expanded into frost-free Mediterranean climates areas.

The cherimoya was introduced to continental Spain from America between the sixteenth and eighteenth centuries with the primary record in 1757. After that, the cherimoya was most likely distributed to Italy, Madeira (Portugal), the Canary Islands, Algeria, and Egypt. The first cherimoya plantation in Italy was in the Reggio Calabria in 1797, and from Italy, it was introduced to Libya, Eritrea, and Somalia (Morton, 1987). After that, it had been grown up in most tropical regions in Asia including in India, Singapore, and Thailand. Fig. 1.

The cherimoya flower is hermaphroditic with a central pyramidal gynoecium composed of up to 300 fused carpels and a basal helical androecium with stamens surrounded by two whorls of three petals. floral dichogamy is the most important characteristic of this species. Cherimoya flowers show protogynous (Wester, 1910), a common feature in Annonaceae (Gottsberger, 1999), and often present in basal/early-divergent angiosperms (Endress, 2015). The hermaphrodite flowers have female and male organs that do not mature simultaneously generally preventing self-fertilization in the same flower. The cycle of the flower is completed in 2 days. In the first day, the flower is in preanthesis, with the petals tightly closed and it passes to the female stage about midday. This phase lasts for 30 h and on the second day the flower switches from the female to the male stage, when the anthers dehisce, around 4–5 pm under Mediterranean conditions. Cherimoya flowers of the same genotype usually open synchronously, and transfer of pollen between different flowers of the same genotype is difficult (Lora et al., 2011). This synchronization is broken by average temperatures $> 22\,^{\circ}C$. The length of stigmatic receptivity increasing humidity and decreasing at higher temperatures (Lora et al., 2011).

Fruit crops within Annona are fleshy and aggregated with several seeds formed mainly by reticulate endosperm and a tiny embryo. Cherimoya fruits are conical or heart-shaped with sweet and juicy white flesh. The skin may be smooth with fingerprint-like markings or covered with conical or rounded protuberances (Schroeder, 1943) (Fig. 2).

The Cherimoya fruit's weight is reported between 200–700 g and its length is between 7.5–12.5 cm (Popenoe, 1974). The flesh is white and sub-acidic and has a delicate and fragrant flavor, such as that of pineapple and banana. There are many seeds in the fruit. (21 to 41 seeds/fruit), which are from 1,5–2,0 cm long and about 1,0 cm wide (manica, 1997) (Fig. 3). Cherimoya fruit is sensitive to browning especially after

Fig. 1. A characteristic plant of *Annona cherimola* Mill. (a) Tree, (b) Fruit, (c) Leave, (d) Flower.

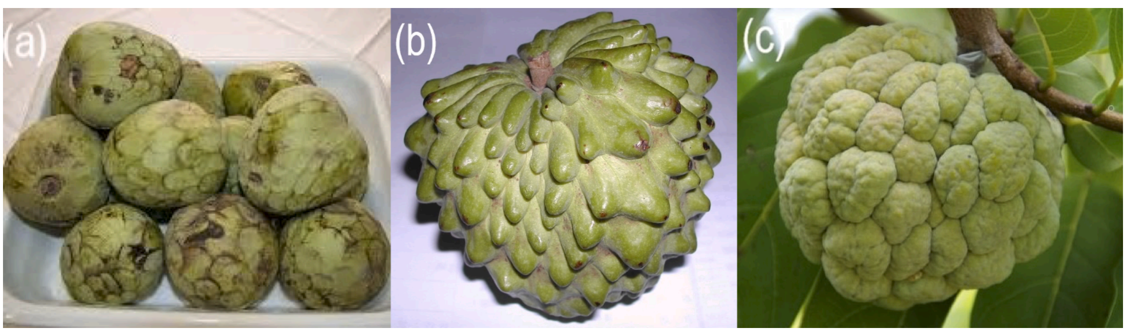

Fig. 2. Typical fruits of *Annona cherimola* Mill. (a) smooth skin with fingerprint-like markings (b) and (c) skin covered with conical or rounded protuberances.

Fig. 3. Longitudinal section of cherimoya fruits.

cutting (Martinez et al., 2015). Browning occurs very fast at normal temperature so Cherimoya fruit should be kept at low temperature (about 10 °C) after harvesting. It induced a very significant oxidative reaction resulting in a loss in the quality of fruits (Amiot et al., 1997). And also, splitting is a phenomenon that often occurs around the peduncle and radiates out from the fruit base during cherimoya fruit ripening (Paull, 1996).

Due to rapid climacteric ripening, the cherimoya fruits are perishable. Storage between 10–12 °C can slightly delay the ripening and therefore extend the shelf life of the fruits (Sevillano et al., 2010).

The fruit of the *Annona cherimoya* is climacteric and only when the pulp has a sufficient degree of softness does the fruit become edible. This characteristic is not reached on the plant, but after 3–6 days of harvesting a temperature between 16 °C and 20 °C. Lower temperature irreversibly stops ripening. The fruits must therefore be harvested before physiological ripening when the color changes from green to light yellow and are left to ripen at room temperature The fruits of Annona cherimola are mainly intended for the fresh market and for this reason they must have high-quality characteristics, especially as regards pomological and sensorial parameters. Compared to other fruits, ripening occurs rapidly in the cherimoya. Cherimoya will ripen in 6–7 days At room temperature (Gardiazabal and Rosenberg, 1986). This is one of the reasons that greatly limit the market potentiality for this fruit.

However, on an island like Sicily, where the distances between the major absorption centers are short, the hypothesis of a large consumer market would still be plausible. Commonly the Annona propagates by seed, which has determined the diffusion of very heterogeneous plants. In recent years, however, vegetative propagation is taking hold, especially through the practice of grafting. To date, the world's largest producer of Annona is Spain, where the most common cultivars are Campas and Fino de Jete. The latter is also the best known and most widespread cultivar in the world (Alique and Oliveira, 1994). Currently, there are no official data that allow quantifying the production of this fruit in Italy. However, production remains very limited because there are very few companies that cultivate this fruit. On the other hand, there are few orchards, mostly citrus trees or other promiscuous arboretums in the regions of Sicily and Calabria. In Sicily, in addition to the aforementioned Fino de Jete, local ecotypes are cultivated whose diffusion is limited to the areas of origin. It seems that custard fruit was used as an "active" ingredient in the Inca diet (Loizzo et al., 2012). On the other hand, this fruit, also today, finds several applications in traditional medicine thanks to its antibacterial and insecticidal properties and in the treatment of digestive disorders and skin diseases (Amoo et al., 2008).

4. Genetics, cytology, and geographic distribution

The genus Annona belongs to the Annonaceae, a family containing some fruit tree crops, such as cherimoya (Annona cherimola), pawpaw (Asimina triloba (L.) Dunal), sugar apple (Annona squamosa L.), the hybrid atemoya (A. cherimola × A. squamosa). Annonaceae is the largest family among the early divergent angiosperms. Although it has a great interest in the evolutionary and taxonomic perspective, cytogenetic works are rare. Although hybrid atemoya has been documented as diploid, a progeny obtained from an interspecific cross between A. cherimola and A. squamosa analyzed with flow cytometry and karyotype analysis highlighted an unusual ploidy variation (Martin et al., 2019). On the other hand, the progeny obtained from intraspecific crosses of A. cherimola revealed polyploidy in a percentage of 2.5 to 33%, while the hybrid atemoyas (obtained with an interspecific cross) revealed 35% of triploidy.

Pollen analysis has been conducted in the cross progeny and their parents to investigate the presence of non-reduced gametes (Martin et al., 2019). Great variability was observed in pollen grain size within the interspecific progeny with enhanced production of unreduced pollen in triploids compared to diploids. PCR analysis showed that 13.7% of the pollen grains from the diploids have two alleles. 41.28% of the grains from the triploids amplified two alleles and 5.63% showed up to three alleles (Martin et al., 2019). This suggests that the larger pollen grains could correspond to diploid and, in a lower frequency, to triploid pollen. Pollen performance was also affected by lower pollen germination in the hybrid triploids with respect to both diploid parents. The results confirm a higher percentage of polyploids in the interspecific cross, affecting pollen grain size and pollen performance. The occurrence of unreduced gametes in A. cherimola, A. squamosa, and their interspecific progeny that may result in abnormalities of ploidy such as the triploids and tetraploids observed by Martin et al. (2019), opens an interesting opportunity to study polyploidy in Annonaceae. Genetic characterization of 1765 accessions of *Annona cherimola* (Mill.) was performed using nine highly informative microsatellite markers. The analysis of these data suggests a Mesoamerican origin of the crop with a possible movement of the plant germplasm between Central and South America in pre-Columbian times (Larranaga et al., 2017). In addition, another study showed a total of 222 alleles of simple sequence repeats (SSRs) in cv. Fino de Jete. They were analyzed using an enrichment of CT/AG repeats of genomic libraries digested with HaeIII and RsaI (Escribano et al., 2008). The heterozygosities were 0.08–0.73 and 0.20–0.84. All this genetic information was used to identify a subset of SSR in the family of Annonaceae to promote the exchange of data among different research groups. The karyotype of *Annona cherimola* ($2n = 14$) was characterized by combining in situ hybridization techniques, fluorochrome banding, and karyomorphological methodologies. 45S and 5S rDNA sites are co-localized where secondary constrictions of the SAT-chromosome pair are present (Falistocco and Ferradini, 2020). The presence of s-GISH signals together with DAPI banding implies that these sequences represent the components of centromere heterochromatin in this species. The karyotype of *A. cherimola* could be used as a reference for the genetic study of all the other members of Annonaceae.

Pollen performance is a key factor for fertilization success. However, changes in pollen production within the same or among species take place in different years and under changing environmental conditions. *Annona cherimola* is characterized by a variable production of bicellular and tricellular hydrated pollen grains at anther dehiscence. It was observed that this phenomenon depends on changes in temperature. The generation of these two different types of pollen is a peculiar feature of cherimoya among angiosperms, making this plant a good model for the study of the effects of climate change on key reproductive features such as pollen performance during the last stage of its development. Temperatures higher than 30 °C typically reduce pollen germination, while lower temperatures have much fewer effects on pollen germination, excluding the great effect on starch hydrolysis (Lora et al., 2012). On the other hand, low water stress enhances the rate of mitosis II, while more drastic drought conditions stopped starch hydrolysis and shorten pollen germination. Taken together these findings show a great effect of environmental conditions on several pollen features during the last phases of pollen development. These changes have a great effect on pollen behavior explaining the high variability observed in pollen tube formation (Lora et al., 2012). Most flowering plants are characterized by producing pollen as monads. But the possibility to produce aggregated pollen is a feature that has evolved several times during angiosperm evolution. Annona has another very important characteristic at the evolutionary level regarding pollen aggregation. Annona is characterized by a pool dispersed in a group of four and it represents a good model to understand how pollen ontogeny may explain the occurrence of this character. Pollen grouping may be caused by minor developmental changes that have been positively favored by natural selection to allow pollen transfer and protection from water stress. A previous study has investigated the molecular modifications of pollen from anther starting differentiation to pollen dehiscence (Lora et al., 2009). Results showed that several collapses during tetrad disintegration may produce a common recurring phenotype that has evolved in new genotypic features when environmental conditions favored the occurrence of pollen transfer (Lora et al., 2009).

The spatial distribution of genetic diversity is an important factor for the conservation of plant genetic resources. Previous work used Geographic Information Systems (GIS) to study this feature in *Annona cherimola* Mill. integrating molecular markers data. This work allows to gain insight into the genetic diversity of cherimoya in South America using SSRs and develop important conservation strategies for the in-situ conservation of the plant germplasm (Van Zonneveld et al., 2012). A variability in allelic presence and high heterozygosity was observed in southern Ecuador and northern Peru, the region that is considered the center of origin of this species. On the other hand, diversity in southern Peru and Bolivia is relatively low. The Annona flower cycle and anatomy have been studied in consideration of the changes in temperature and humidity that typically drive modifications on stigmatic receptivity (Lora et al., 2011).

The inbreeding phenomenon has been hampered by several mechanisms developed in different angiosperm taxa during their evolution such as the dichogamy and the maturation of male and female reproductive structures at different times. The understanding of the consequences of outbreeding will contribute to the understanding of the role of these key phenotypic changes in the evolution of angiosperms. The analysis showed a high quantity of seeds obtained by self-fertilization in spite of the dichogamous system. This implied that stigmatic receptivity is a phenotypic feature affected by environmental factors such as high temperatures and high humidity. This entailed that geographic and temporal sexual disjunction of sexual system inhibits selfing and those environmental circumstances could promote enhancement of selfing to insure reproductive assurance (Lora et al., 2011).

5. Key metabolites in Annona's different parts

Most of the works dealing with the investigation of phytochemical healthy components of the cherimoya fruit determined the total polyphenolic content and radical-scavenging and antioxidant activity of extracts obtained from various parts of the fruit (Gupta-Elera et al., 2011; Loizzo et al., 2012). The available data shows that this fruit is an interesting source of antioxidant molecules, containing good amounts of vitamin C, vitamin E, and polyphenols (Loizzo et al., 2012; Roesler et al., 2006) (Fig. 4).

The most important families of phenolics present in cherimoya fruit pulp are flavan-3-ols, (*epi*)catechin and their derivatives (procyanidins such as Locatechin, (*epi*) gallocatechin, (*epi*)afzelechin-(*epi*)catechin Procyanidin) (Santos et al., 2016; Barreca et al. 2011). Fruits are rich in acetogenins, proanthocyanidins (C. Gentile et al., 2020; Durán et al., 2021). The major volatile compounds identified in the fruit include methyl butanoate, butyl butanoate, 3-methylbutyl butanoate, 3-methyl butyl 3- methyl butanoate, and 5-hydroxymethyl-2-furfural. Annona fruits contain enzymes that are highly active against pathogenic fungi of crops. Two cold-induced chitinases were purified from the mesocarp fruits and revealed to have biochemical features similar to acidic endochitinases with a molecular weight of 24.79–47.77 kDa and to belong to the glycosyl hydrolases family. One of them, AChi24 showed to be active as an antifungal defense against *Botrytis cinerea*. The two acidic endochitinases seem to be induced at low temperatures in subtropical fruits (Goñi et al., 2013). A previous study has identified 40 metabolites in fruit pulp belonging to different categories such as terpenes, esters, alcohols, fatty acids, and carbonyl compounds (Ferreira et al., 2009). It showed that the quantitative levels of these metabolites and other volatiles allow greatly to distinguish each cherimoya cultivar from the others (Ferreira et al., 2009). In a recent study (Santos et al., 2016), kaurene diterpenes, fatty acids, and sterols were showed to be the principal lipophilic metabolites in the pulp of four cherimoya cultivars from Madeira Island, that were studied for the first time. Kaur-16-en-19-oic acid was the most present lipophilic component of all cultivars in the dry component. High levels of flavan-3-ols, such as galloylated and non-galloylated compounds were found. Catechin, (*epi*) gallocatechin, (*epi*)catechin-(*epi*)gallocatechin, (*epi*)afzelechin-(*epi*) catechin and procyanidin were identified. Two cultivars ('Mateus I' and 'Mateus III') contain the highest levels of phenolic compounds. Fresh *Annona cherimola* fruits revealed ent-kaurane diterpenoids such as (16R)-ent-kauran-17,19-diol, (16S)−17-hydroxy-ent-kauran-19-oic acid, (16R)−17-hydroxy-ent-kauran-19-oic acid, and (16R)−17-dimethoxy-ent-kauran-19-oic acid (Miyashita et al., 2010). Cherimoya fruits from Almuñécar (Granada, S Spain) was shown to contain a high nutrient contents, especially K, Ca, Fe, and Zn (García-Carmona et al., 2020).

Phytochemical analyses in leaves of different cultivars of Annona cherimola showed high levels of phenolic metabolites, such as proanthocyanidins, flavonoids or alkaloids. Antioxidant activities were found for polyphenols, and antiproliferative action was observed against HeLa and HepG2 cell lines (Mannino et al., 2020). These beneficial properties were linked with alkaloid levels. *Campas* and *Torre 1* showed high content in alkaloids and, considering the anti-proliferative properties of their extracts, we may speculate their beneficial use as dietary supplements due to their chemo-preventive effects (Mannino et al., 2020). The

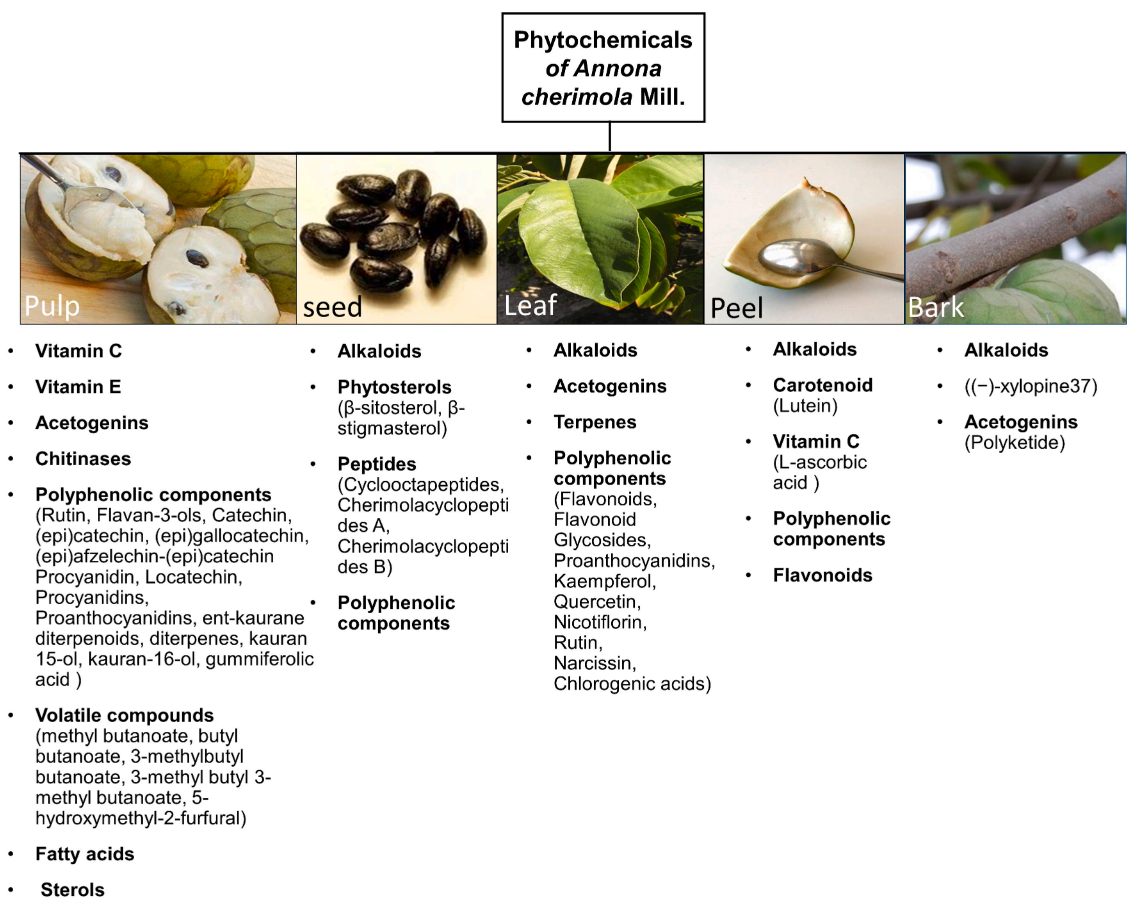

Fig. 4. Categories and singular phytochemicals identified in different plant tissues of *Anna cherimola* Mill.

chemical profile of cherimoya leaf extracts has been determined using NMR and HPLC-TOF-MS (Díaz-de-Cerio et al., 2018). A total of 77 compounds have been characterized and 12 were in common between the two techniques. Flavonoids were present in high quantity. The combined use of LC—HRMS and NMR showed to be a good method to gain insight into the comprehensive metabolite composition of cherimoya. Leaves contain high levels of phenolic compounds (flavonoids (rutin and chlorogenic acids)) (Díaz-de-Cerio et al., 2018). Among flavonoids, the following were detected: kaempferol, quercetin, nicotiflorin, and rutin (Calzada et al., 2017). This latter is a major flavonol glycoside of the leaves of *A. cherimola*. (Calzada et al., 2020) Interestingly, the fermented juice of *Annona cherimola* Mill. seems to be a functional beverage with important nutritional and functional features (Isas et al., 2020).

The main toxic substances of the seeds are the annonaceous acetogenins (ACGs) (Haykal et al., 2019) ACGs extracted from *A. cherimola* seeds have cytotoxic effects on the prostate, breast, and colon cancer cell lines, with a 10,000 times stronger potency than adriamycin, that is an important chemotherapeutic medicine (Kim et al., 2001). Seeds contain β-sitosterol and β-stigmasterol, cyclooctapeptides, and cherimolacyclopeptides A and cherimolacyclopeptides B.(Haykal et al., 2019). In a recent study on the dried seeds of M. oleifera, A. cherimola presented compounds with both antioxidant and antitumor activity. The secondary metabolites have polar nature such as phenolic compounds, terpenoids, glycosides, saponins, and polyketides. Within the group of phenolic compounds, flavonoids (flavones, flavanones, and flavanols), phenolic acids, and phenylpropanoids were particularly present. In addition acetogenins were identified, in the A. cherimola ethanolic extract (Fuel et al., 2021).

Fruit peel presented high levels of carotenoids(lutein) and vitamins (L-ascorbic acid). The polyphenolic profile of peel, pulp, and seeds of cherimoya fruits of the Campas and Fino de Jete cultivars was evaluated through the HPLC-DAD-ESI-QTOF-MS technique. The results of this study highlighted a significant presence of polyphenols of the flavan-3-oil group, such as epicatechins and their derivatives (proanthocyanidins). The peel is among all parts of the fruit the richest in polyphenolic components, followed by seeds and pulp (García-Salas et al., 2015). Among pulp, peel, and seeds of four cultivars from *A. cherimola* Mill, the peel of Madeira cultivar exhibits high antioxidant capacity, and great levels of flavonoids. Relating to carotenoids, lutein was the most present, with a concentration ranging from 129 to 232 μg/100 g. It has been shown that the peel of the cherimoya fruits from Almuñécar (Granada, S Spain) was enriched in K, P, C, and N and also, had considerable contents of Ca and Mg (García-Carmona et al., 2020).

Annona stems are also rich in acetogenins, secondary lipophilic metabolites of the polyketide family, with documented antioxidant, anti-inflammatory, and antiproliferative activities (Chen et al., 1999). A bis-THF ring acetogenin, aromin-A, and the cytotoxic acetogenin squamocin have been already isolated in the stem of cherimoya more than 20 years ago (Chen et al., 1999).

By using the by gas chromatography-mass spectrometry (GC / MS), the chemical composition of the essential oils of the fresh leaves, flowers and fruits from Annona cherimola was analysed. Bicyclogermacrene, trans-caryophyllene and δ amorphene were major constituents in the oil of the leaves. Bicyclogermacrene, α-terpinolene and germacrene D were the major constituents in the oil of the flowers and β-pinene, α-terpinolene, β-fenchyl alcohol and α-pinene were the major constituents in the oil of the fruits (Yolanda Ríos et al., 2003).

6. Healthy properties of *Annona cherimola* Mill

It seems that custard fruit was used as an "active" ingredient in the Inca diet (Loizzo et al., 2012). On the other hand, also today this fruit finds several applications in local traditional medicine for its antibacterial and insecticidal properties and in the treatment of digestive disorders and skin diseases (Amoo et al., 2008).

The extended range of different metabolites has important healthy properties against several degenerative and chronic human diseases (Table 1, Fig. 5).

6.1. Diabetes

Alpha-glucosidase inhibitors (AGIs) are interesting bioactive chemicals, thanks to their therapeutic action against type 2 diabetes mellitus and viral infections. The use of *Annona cherimola* has been reported in Mexican traditional medicine to cure diabetes. Ethanolic extracts were tested for their effects on alloxan-induced type 2 diabetic (AITD) in a rat study (Vasarri et al., 2020). Rutin, present in high concentration in cherimoya extracts, showed to be an important α-glucosidase inhibitor due to its antihyperglycemic activity. The in vitro anti-glycation and anti-α-glucosidase activities of pulp extract were studied using the enrollment of healthy and diabetic subjects. The effects of pulp intake on

Table 1
Nutraceutical, antioxidant, therapeutic characteristics again degenerative and chronic diseases. The metabolite, type of action, experiment details, and references.

Metabolic compounds or mixture	Type of action	Tissue	Type of evidence: in vitro, in vivo traditional medicine, the total content	References
Acetogenins	Antioxidant, Anti-inflammatory, and Antiproliferative	Stems	In vitro, in vivo	Chen et al., 1999
Terpenes, Esters, Alcohols, Fatty acids, and Carbonyl compounds	Antioxidant	Leaves, Fruits	In vitro	Ferreira et al., 2009
macro-and micro-nutrients and Polyphenols	Antioxidant, nutritional, and nutraceutical	Fruits	Total content	C.
Proanthocyanidins, Flavonoids, and Alkaloids	Antioxidant and antiproliferative	Fruits	In vitro, the specific and total content	Mannino et al., 2020
Polyphenols in general	Antioxidant	Fruits, seeds, and pulp	In vitro	García-Salas et al., 2015
Polyphenols	Antiproliferative	Seeds, bark tissues	In vivo	A. ; García -Salas et al., 2015
Uncharacterized, all complex	Healthy general properties	Fruits	Traditional medicine	Loizzo et al., 2012
Uncharacterized, all complex	Antibacterial and insecticidal, against digestive disorders and skin diseases	Fruits	Traditional medicine	Amoo et al., 2008
Flavonoids	Healthy general properties	Leaves	In vitro	Díaz -De-Cerio et al., 2018
Flavonoids	Antioxidant	Fruit peel	In vitro	Albuquerque et al., 2016
Kaurene diterpenes, fatty acids, flavan-3-ols, and sterols	Antioxidant	Fruits	In vitro	Miyashita et al., 2010
Chitinases	Anti-microbial	Fruits	In vivo	Goñi et al., 2013
Rutin	Anti-diabetes	Fruits	In vivo, In vitro	Vasarri et al., 2020

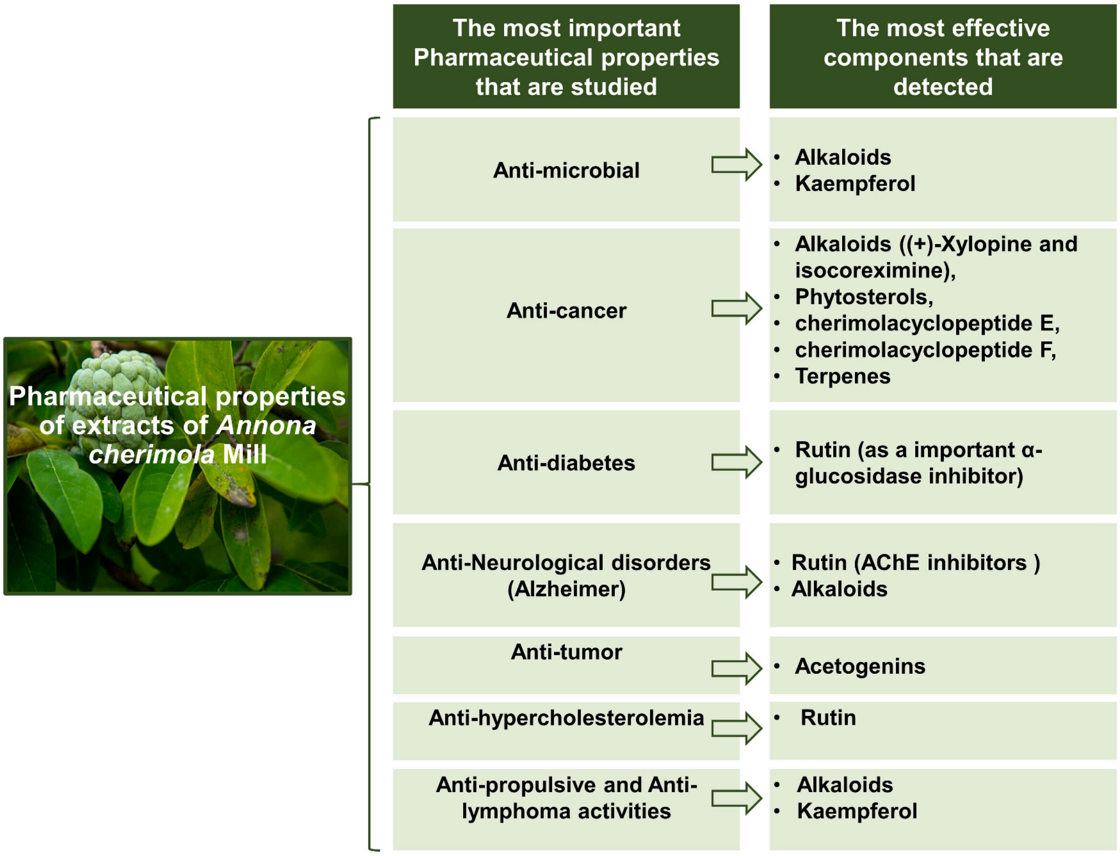

Fig. 5. Pharmaceutical properties of extracts of *Annona cherimola* Mill. Type of activities and classes of diseases were indicated. The arrow is directed toward the beneficial pharmaceutical with more in vitro and in vivo evidence.

postprandial glycemia were investigated. Data revealed that the extract significantly reduced albumin glycation in vitro and repressed the activity of the α-glucosidase enzyme. In addition, the ingestion of pulp does not affect levels of postprandial glycemia, rendering it a suitable source of health-promoting phytonutrients as well as a potential functional food to prevent or limit diabetes. These data confirmed the well-known fame of *A. cherimola* for the therapy of diabetes (Vasarri et al., 2020). A rapid procedure for detection and identification of AGIs in cherimoya fruit (*Annona cherimola* Mill.) using high-performance thin layer-chromatography (HPTLC) associated with bioassay and mass spectrometry (MS) was developed (Galarce-Bustos et al., 2019). Coupling HPTLC-MS and ultra-high-performance liquid chromatography (UHPLC)-diode array detector, three AGIs were identified in Annona peel tissues and seeds. The identification of these metabolites was performed with tentative assignments as phenolamides (Galarce-Bustos et al., 2019).

In a recent study, the analysis of tea infusion extracts by HPLC identified rutin as the major component showed that Annona cherimola tea infusions of the leaves can be used in the treatment of diabetes suggesting that rutin may be responsible for these properties (Martínez-Solís et al., 2021).

6.2. Anti-microbial properties

Results revealed that kaempferol present in Annona leaves was the most abundant antiamoebic and antigiardial metabolite, especially against *Entamoeba histolytica* and *Giardia lamblia*. This molecule showed an interaction with ferredoxin oxidoreductase, a pyruvate enzyme, in a site different from the one interacting with metronidazole. This confirmed the effectiveness of the traditional use of Annona extracts to cure diarrhea and dysentery caused by protozoal agents (Calzada et al., 2017). Other alkaloids of cherimoya (liiriodenine, anonaine, asimilobine) presented anti-microbial activities against *Staphylococcus epidermidis* (Nugraha et al., 2019).

The essential oils of leaves, flowers and fruits from A. cherimola, showed antimicrobial activity against five Gram (±) bacteria and one fungus (Staphylococcus aureus, Enterococcus faecalis, Escherichia coli, Shigella sonei, Proteous mirabilis, Candida albicans) (Yolanda Ríos et al., 2003).

6.3. Anti-cancerogenic action

Previous results revealed high levels of three flavonoid glycosides (rutin, nicotiflorin, and narcissin) in Annona leaves, especially rutin (24.5 mg/g of extract). The ethanolic extract of the leaves of *A. cherimola* showed antipropulsive and antilymphoma activities (Calzada et al., 2020).

Antiproliferative activity of ethanol seed extract of cherimoya was evaluated against the human stomach gastric adenocarcinoma (AGS) cell line and the normal lines of the human gastric epithelial cell (GES-1) (Macuer-Guzmán et al., 2019). The extract showed an IC_{50} of 80.43 μg/mL in AGS cells. A selectivity index (SI) more than three times higher than cisplatin was observed. The cherimoya seed extract revealed induction of apoptotic activity in AGS cells. These data should be confirmed by validation experiments to be performed in vivo. In addition, another study confirmed the anti-cancer action of cherimoya. Two novel cyclic peptides, cherimolacyclopeptide E (1) and cherimolacyclopeptide F (2), showed significant cytotoxic action against human nasopharyngeal carcinoma with cell culture experiments (Wèlè et al., 2005). These peptides were analyzed using MS/MS fragmentation experiments and a Q-TOF mass spectrometer equipped with an ESI source. In addition, 2D NMR analyses and chemical degradation assay were executed (Wélé et al., 2005). Seed extract effects on another type of cancer, Acute Myeloid Leukemia (AML), were also studied in experiments in vitro. Seed ethanolic extract significantly inhibits the proliferation of different AML cell lines. DNA fragmentation and positive staining for Annexin V showed an enhancement of apoptotic cell death through the induction of pro-apoptotic proteins modulating both intrinsic and extrinsic apoptotic pathways (Younes et al., 2020). Phytosterols presence was observed using GC/MS analysis, together with the presence of other well-known bioactive compounds. Extracts of *Annona cherimola* Mill seed revealed a potent toxic action, affecting apoptosis in AML cell lines through the enhancing of both the extrinsic and the intrinsic pathways (Haykal et al., 2019). Leaf extracts showed anti-cancer and anti-proliferative activities on Acute Myeloid Leukemia (AML) cell lines and this might be due to the high content of terpenes that showed anti-proliferative responses and promotion of apoptotic crosstalk on AML cell lines (Ammoury et al., 2019).

Annona cherimola extract has been reported to have a significant effect on AML (acute myeloid leukemia) cell proliferation. This highlighted the protective effects of tea made from *A. cherimola* leaves in the treatment of cancer (Haykal et al., 2021).

It has been demonstrated that A. cherimola extract inhibits the clonal expansion of a mutant of Saccharomyces cerevisiae by inhibition of topoisomerase I (22%). The characterization of the extracts of cherimoya pulp by GC/MS revealed the presence of two diterpenes of the family of Kaurenes (kauran 15-ol and kauran-16-ol) and gummiferolic acid, which have demonstrated antiproliferative activity through the inhibition of topoisomerases in other studies (Razura-Carmona et al., 2021).

Particularly, compounds as (+)-Xylopine and isocoreximine, revealed significant anti-cancer action against A549 and K-562 cell lines. Taken together, alkaloids from Annona genus showed to be highly diverse in their structure and pharmacological action, with a great potential for promoting novel anti-infective and anticancer therapeutic treatments (Nugraha et al., 2019). Interestingly, another closely-related species of the Annonaceae family, *Annona muricata* L. has been traditionally included among plants that may have anticancer properties (Moreau et al., 2018). The plant is usually eaten as boiled leaves. Interestingly, it has been used as chemotherapy for lung cancer as self-medication. These data suggest that several members of the Annonaceae family may have phytochemical activities with beneficial effects on different types of cancers. Annonaceous Acetogenins (ACGs) isolated from this plant are lipophilic polyketides and seem to be only specific to Annonaceae (Nik Mat Daud et al., 2016). They are known as high potent antitumor compounds, although they have the disadvantage of having low solubility Some well-known acetogenins are Molvizarin, cherimolin-1, motrilin, annonacin, and annonisin. They have been found in *A. cherimola* leaves and showed to be a strong anti-tumoral agent against different cells such as HeLa, IGROV-1 (Gutiérrez et al., 2020). Annonacin ACGs were encapsulated in polymer micelles to enhance their solubility in aqueous media. The bioavailability was highly enhanced in the human digestive system if a sufficient level of encapsulation was reached (Gutiérrez et al., 2020). These data revealed that compounds of *A. cherimola*, modified with traditional pharmaceutical technology may be useful anticancer agents to be included in therapeutic formulation against different cancer types.

In a recent study on the dried seeds of M. oleifera, A. cherimola and tuber of T. tuberosum, A. cherimola and M. oleifera extracts presented the lowest IC50 in T-84 and HCT-15 (resistant) cells, respectively, as well as the highest level of inhibition of proliferation in multicellular tumor spheroids of HCT-15 cells. In vitro assays revealed that all the ethanolic extracts possessed moderate antioxidant capacity and a high antiproliferative capacity against colon-rectal cancer (CRC) cell cultures as monolayers and MTSs. Therefore, although in vivo testing will be necessary, ethanolic extracts from M. oleifera, T. tuberosum, and A. cherimola are becoming new therapeutic options. These extracts could be used either alone or in combination with other antitumor agents, for the prevention and treatment of CRC (Fuel et al., 2021).

The ethanolic extract of Annona cherimola leaves showed promising and interesting anticancer activity, mostly on melanoma cell line, without exerting cytotoxicity on the normal cells. Finally, numerous bioactive compounds, responsible of the antioxidant and antitumoral properties, were identified in the studied extracts (Fuel et al., 2021).

6.4. Therapeutic against Neurological disorders

Acetylcholinesterase (AChE) inhibitors are well-known to be effective in the cure of Alzheimer's disease and other neurological disorders. Cherimoya peel showed to be a potent inhibitor of neurological disorders, probably due to the high presence of alkaloids with AChE inhibitory properties (Galarce-Bustos et al., 2019). A previous study has detected and isolated AChE inhibitors in cherimoya using high-performance thin-layer chromatography (HPTLC) coupled with bioassay-mass spectrometry (MS) and other methodologies (Galarce-Bustos et al., 2019). *Annona atemoya* is a spontaneous hybrid of *Annona cherimola* and *Annona squamosa* found in subtropical or tropical regions. Leaf extracts of this hybrid showed inhibitory effects on the mechanisms of pathogenesis of Alzheimer's disease (Lim et al., 2019). The ethanolic extract reduces the amyloid-β (Aβ) aggregation and has antioxidant activity. They also showed beneficial effects against neuronal cell death in HT22 hippocampal cells. The oral ingestion of the extract reduced memory loss and repressed the expression of markers of Alzheimer's disease-related disorders in mice. Leaf extract also showed to protect from oxidative stress, neuronal cell death, and memory impairment (Sohn et al., 2019). Experiments using antibody microarray analysis showed that epidermal growth factor receptor was induced in neuronal cells in mice. The technique of high-performance liquid chromatography showed that rutin is highly present in the extract of this Annona hybrid and together with isoquercitrin revealed inhibitory action on Aβ aggregation (Kazman et al., 2020). This evidence demonstrated that rutin is a bioactive compound against Alzheimer's disease. This effect was caused by the action of the epidermal growth factor receptor/G protein-coupled receptor kinase 2 pathway. These activities were even higher than other extracts from previously characterized medicinal plants (Kazman et al., 2020). These data showed that the extract of species of the family Annonaceae may be the basis of future drug development for neurological disorder treatment. Future studies are required to perform similar experiments using *Annona cherimola* extract.

6.5. Iper-cholesterolemia

Leaf decoctions of *Annona cherimola* Mill. are known to be commonly used in Azores islands to cure hypercholesterolemia (Mannino et al., 2020). Rutin seems to be the main component with significant activity against hyper-cholesterolemia. In addition, the ingestion of *Annona cherimola* extracts did not alter the bioactive properties during gastrointestinal digestion, as shown in experiments in vitro. The Annona extract was effective in reducing cholesterol absorption in experiments on Caco-2 cell lines. In addition, HMG-CoA reductase activity was reduced by half when using the extract. Rutin, tested pure at a concentration similar to that present in the cherimoya extract, was effective in diminishing cholesterol absorption through Caco-2 cells monolayer. The IC50 of rutin was 17.85 μM. The results confirmed the validity of the traditional use of leaf decoctions of *Annona cherimola* due to the repression of HMG-CoA reductase activity (Falé et al., 2013).

Methanolic extract of Annona cherimola was evaluated for its anti-hyperlipidemic potential. A significant dose dependent decrease was observed in plasma total cholesterol, triglycerides and LDL-cholesterol. At the same time considerable increase in HDL-cholesterol levels was observed upon administration of methanolic extract at the dose of 250 mg/kg and 500 mg/ kg. Atherogenic index as well as LDL/HDL cholesterol ratio was lowered significantly in case of methanolic extract treated groups compared to normal control which reflects the anti-hyperlipidemic potential of Annona cherimola. (Verma et al., 2011)

6.6. Anti- gastro ulcerative

Rats fed with the leaves and bark ethanolic extract of A. cherimola showed improvement in ulcer index, oxidative stress markers, cell organelles marker enzymes as well as the histology of stomach. In conclusion, the bark and leaves ethanolic extract of Annona cherimola recorded the most in vitro antioxidant effect and served as protective gastroulcerative agents. In conclusion, rats fed with A. cherimola extracts showed improvement in ulcer index, oxidative stress markers and cell organelles markers enzymes as well as the improvement of the histopathological pattern in gastric mucosa. The presence of phenolics and flavonoids improved the selected parameters due to their antioxidant effects as well as its role as anti-ulcerative agent (Mohammed et al., 2020). Methanolic and aqueous extracts of 53 different plant species (49 genera in 29 families) used in Mexican traditional medicine to treat gastrointestinal disorders were screened in vitro for their anti-Helicobacter pylor activity. Methanolic extracts of Persea americana, Annona cherimola, Guaiacum coulteri, and Moussonia deppeana (MIC <7.5 to 15.6 g/ml) showed the highest inhibitory effect (Castillo-Juárez et al., 2009).

7. Conclusions

A. cherimola Mill. is a tropical tree that has gained high-interest thanks to the identification of several phytochemicals with healthy properties that confirmed its well-known fame in traditional medicine. This plant is not only a natural source of food but is an important medicinal plant. This plant, like several others of the Annonaceae family, has been shown to carry a wide range of biological properties. Promising applications of plant extracts of *A. cherimola* are as anticancer, anti-chronic and degenerative diseases, antioxidant in general, and as a natural pesticide. Most of the research works were performed to test the biological activities of the plant extract, while further studies are required to better characterize the biochemical and physiological actions of these compounds. It will also be important to elucidate the underlying mechanisms modulating these activities. This is absolutely essential for the development of pharmaceutical and agricultural applications. Furthermore, clinical trials are required to determine the rich pharmaceutical potential of *A. cherimola* to cure the neurodegenerative disorder. Taken together, a good number of scientific works in the international journal's databases demonstrate that *A. cherimola* Mill. could be an important natural source of phytochemicals with highly beneficial antioxidant, antiproliferative and anti-chronic, and anti-degenerative diseases. This opens the possibility to develop new therapeutic treatments against tumors and other severe degenerative human diseases including in formulated preparations with highly active phytocomponents. These healthy metabolites are present in different plant tissues although there is preferred accumulation of some classes of these compounds in fruit peel and leaves (terpenes). Polyphenols (seeds and fruit), anti-microbial enzymes (leaves), acetogenins (fruit and leaves). Additional efforts are needed to identify all the high spectrum of metabolites contributing to these properties. These future new investigations will determine the concentration at which this beneficial effect is caused. We believe that this review will promote research for clinical investigations on the biological activities of *A. cherimola* to produce new effective and sustainable agricultural and pharmaceutical agents.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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