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# *Crassula ovata*: An Updated Review of its Ethanomedicinal Applications, Phytochemical Profile, and Pharmacological Potential

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**Abstract: The genus *Crassula* (family Crassulaceae) contains about 150-200 species of succulent plants that are mainly found in southern Africa, but are also well represented in Europe, the Americas, Australia and New Zealand. Although probably cultivated most famously as houseplants these species have a long history of traditional medicine use by indigenous African peoples and in Asian herbal medicine, where they have been used to treat gastrointestinal illness, epilepsy, diabetes, wounds, skin burns, inflammation, and infections. This review is a comprehensive synthesis of the existing information on the phytochemical composition, pharmacological activities, toxicological profile, and future therapeutic potential of the genus Crassula. Phytochemical studies have shown a wide range of bioactive secondary metabolites, such as phenolic acids (gallic, caffeic, ferulic, chlorogenic acids), flavonoids (quercetin, kaempferol, apigenin, naringenin, catechin), terpenoids, phytosterols (-sitosterol), C-glucosides (ber Pharmacological studies have validated many traditional uses, demonstrating significant antioxidant (DPPH scavenging up to 85% at 200 µg/mL), antimicrobial (broad-spectrum activity against *E. coli*, *S. aureus*, *K. pneumoniae*), antidiabetic, anti-inflammatory (COX-1/COX-2 inhibition by α/β-amyrin), anticonvulsant (delayed seizure onset in PTZ-treated mice), anticancer (cytotoxicity against KYSE-30 esophageal cancer cells); bergenin synergizes with docetaxel in PC-3 prostate cancer cells, inducing $G_0/G_1$ arrest and apoptosis via Bax/Bcl-2 modulation), hepatoprotective, and wound healing activities. Toxicity tests show that in humans, there is mild gastrointestinal irritation, but there is severe toxicity in dogs and cats, which should be taken into account. Future research directions involve detailed metabolomic profiling, in vivo mechanistic, clinical trials, production of biotechnologically through hairy root cultures and investigation of synergistic effect of drug combinations. *Crassula* is a genus with potential to supply new pharmaceutical leads, however, under-explored, a transition between traditional ethnomedicine and evidence-based drug discovery.**

***Keywords:*** *Crassula; Crassulaceae; Phytochemistry; Pharmacology; Bergenin; Traditional Medicine; Antimicrobial; Antioxidant; Antidiabetic; Anticancer; Hepatoprotective; Crassula ovata; Jade Plant*

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## I. INTRODUCTION

*Crassula* is a genus that is one of the most astonishing and varied groups of the angiosperms, and this is a real testament to the strength of evolutionary adaptation. *Crassula*, as the type genus of the Crassulaceae family, or stonecrops or orpine family, represents the key attributes due to which this group of plants has been able to inhabit the most demanding conditions on the Earth. The name of the genus, which is the roots of the Latin word crassus, meaning thick, is the direct reflection of the most characteristic trait of it: the water-storing fleshy leaves [1]. This morphological character is inherently connected with a specific photosynthetic pathway, the Crassulace an Acid Metabolism, which is a water-saving mechanism initially identified and defined in this family. Stomata open at night in CAM plants and capture carbon dioxide that gets stored in the form of malic acid and utilized in daytime photosynthesis, and thus reduces water loss in hot and arid climates [2]. The Crassula genus is, thus, a pivotal stone in our knowledge of the evolution of succulent plants as well as in the physiological ecology and, thus, an object of deep scientific interest. *Crassula* is a genus of flowering plants in the order Saxifragales, and is a subfamily of Crassuloidea [3]. It is a heterogeneous group with an estimated 150 to 200 accepted species, which is constantly changing as taxonomic studies fine-tune the classification Table 1 [4]. It has an exceptionally broad global distribution with native species in Europe, the Americas, Australia and New Zealand. But its centre of diversity is undoubtedly in the southern part of Africa, where it is the most species-rich of

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the crassuloid genera, the equivalent of the heterogeneous genus Sedum of the north [5]. Among the five crassuloid genera native to southern Africa, Crassula is by far the most diverse, with a beautiful arsenal of growth forms, including miniature creepers that grow in soil crevices, large shrubs almost tree-like, and even perennial water plants [6]. This morphological plasticity is one of the reasons of its ecological success and enables it to inhabit a large variety of niches throughout the continent [7]. The evolutionary history of *Crassula* is an interesting story of evolution of recent and rapid adaption. Phylogenetic analyses have established that even though certain lineages are more ancient, much of the diversification of the genus is a comparatively recent event, with a big radiation occurring in the past 10 million years [8]. This speciation burst, which started during the late Miocene, is closely associated with alterations in life-form, and is believed to have been triggered by the expansion of drier climates to southern Africa [9]. The genus is highly labile with regard to life-forms in the sense that it has regularly switched between various growth strategies and this plasticity has been a major force behind its diversification Fig.1. The highest radiation in *Crassula* exhibits various adaptations in arid environments that cement its position as a good model group in examining the evolution of plants under the climate change pressure [10, 11].

Table 1 Taxonomy Hierarchy

| **Taxonomic Rank** | **Scientific Name** |
|---|---|
| Kingdom | *Plantae* |
| Division (Phylum) | *Tracheophyta* |
| Class | *Magnoliopsida* |
| Order | *Saxifragales* |
| Family | *Crassulaceae* |
| Genus | *Crassula* |

This is a highly dynamic evolutionary history that has led to a genus whose taxonomy remains not completely stable, with new species being continually discovered and described, especially in southern Africa [12]. On top of its scientific value, *Crassula* is of great ecological value. In natural environments, where it is a native, especially in the Succulent Karoo of South Africa and other arid areas, it serves as a key constituent of the plant life, frequently in rocky areas, in exposed locations among boulders, and on wet grasslands [13]. These plants are food, shelter and microhabitat to various insects, birds and other animals. They are able to stabilize these volatile ecosystems by their capacity to grow in poor and stony soils as well as full sun. *Crassula* is an important source of pollinators, especially its flowers [14]. Some of these species are small with dull coloured flowers, others are large and brightly coloured aloe like, like the red flowers of *Crassula coccinea*. The inflorescences that are small, head-shaped, and common in the genus supply much needed nectar and pollen to a range of insects as well as adding to the biodiversity of their ecosystems [15]. *Crassula* too has a rich and long history of cultural and horticultural importance, most notably represented by the Jade Plant, *Crassula ovata* [16].

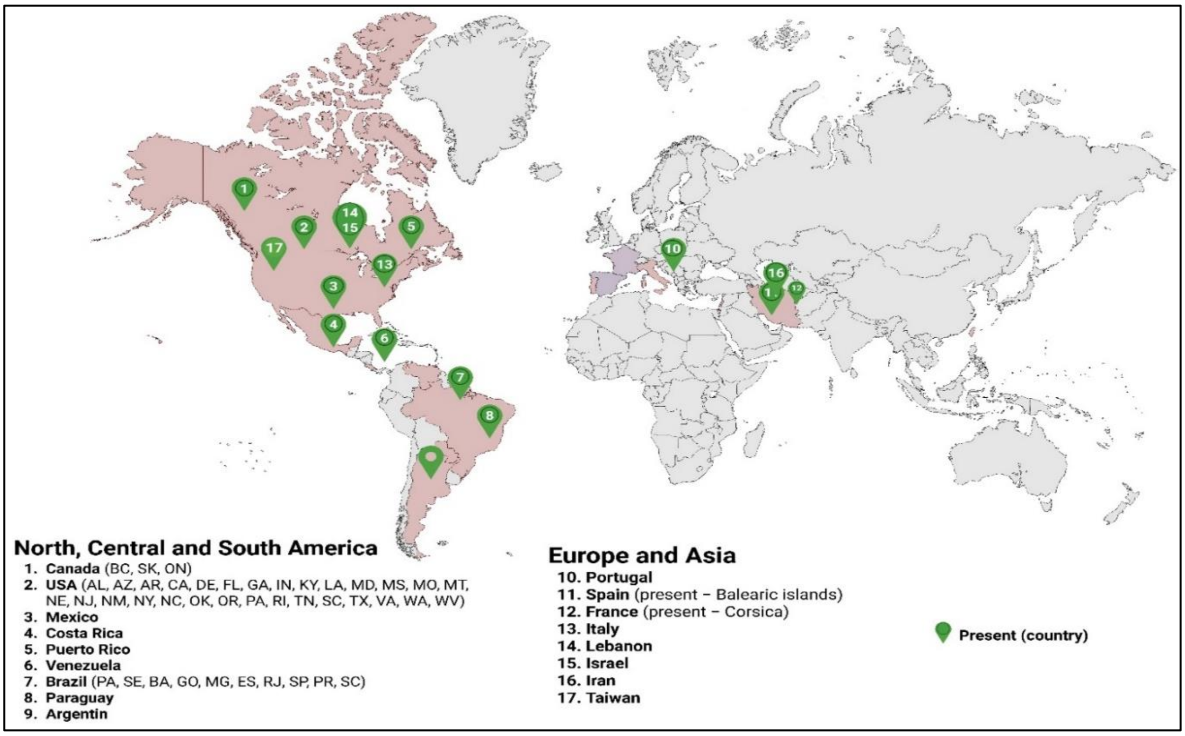

Fig 1 Global Presence of Selected Countries by Region

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This species is indigenous to the Eastern Cape region of South Africa and has over the centuries become one of the most popular houseplants of the world [17]. The fact that it has become a world wide favorite speaks volumes of its amazing hardness; it is a slow growing, hard, and uninspiring plant that is an excellent companion to both the amateur and professional gardener. The heavy, shiny and coin-shaped leaves of the plant have given it a host of nicknames Money Plant, Penny Plant, Dollar Plant, and Lucky Plant and the plant is often grown as a living amulet of prosperity, good fortune and good energy. It is a highly ingrained symbolism within most cultures, especially in Asia, where they believe it is good feng shui to have a Jade Plant near the front door of a house in order to bring prosperity. The plant's popularity has also given rise to a plethora of cultivated varieties with different leaf shapes and variegations, further cementing its status as a beloved ornamental staple [18]. Different *crassula* species mentioned in Fig.2.

Deep rooted in traditional medicine, the genus *Crassula* has long been a part of the traditional medicines of Africa, especially in its native land. There is a rich ethnobotanical folklore of the records of the medicinal uses of these succulents, which have been transmitted across generations [19]. In some areas, leaf juice is used to treat epilepsy and diabetes, and the Basotho people use some of the parts of the plant in charms. Contemporary scientific studies are starting to confirm these traditional applications. Phytochemical studies have shown that *Crassula* is a good source of bioactive substances, such as phenolics, sterols, and triterpenes. Research has verified that *Crassula* extracts have a variety of biological activities such as anticonvulsant, antiarthritic, antimicrobial, antioxidant, and antidiabetic. As an example, extracts of *Crassula arborescens* have been shown to have anticonvulsant activity in animal models and single compounds such as gallic acid and quercetin have been shown to have strong anti-oxidant and anti-inflammatory effects *in vitro*. This combination of folk wisdom and science underscores the promise of the genus in providing new pharmaceutical agents [20].

Nonetheless, the very adaptations that have rendered *Crassula* so robust and successful pose a significant challenge when some species are introduced into the non-native environment. Although the genus is not necessarily invasive everywhere, certain species have turned into infamous ecological weeds [21]. An amphibious succulent native to Australia and New Zealand, it is a very destructive invasive species in parts of Europe, especially the United Kingdom, where its sale has been prohibited. Its submerging, emergent and terrestrial capabilities and its spread by tiny fragments of stems enables it to produce dense, smothering mats that outcompete indigenous vegetation and modify aquatic environments. The thick mats have the potential to cover water bodies entirely, obscuring the submerged vegetation and leading to harmful transformations in the zooplankton, macro-invertebrate and fish population. This scenario is a difficult and expensive issue to conservation managers who are using techniques like control of water levels, wrapping of plants to prevent sunlight and even considering the use of biological control agents to contain the infestations [22].

Ironically, the popularity of *Crassula* among horticulture in foreign countries that makes it an admirable houseplant is a threat to the wild species as well. Illegal harvesting of wild Crassula plants due to demand of rare and unusual succulents has driven some of them to extinction [3]. The seriousness of this threat is highlighted by a number of confiscations of illegally collected *Crassula* species, such as during a South African police operation named Operation *Crassula*. An example is *Crassula simulans*, which is on the SANBI Red List as Vulnerable due to only five locations, and may be at risk due to habitat loss and invasion by alien plants. Having limited known populations, a species with a bad recruitment and recovery capability could easily be driven to extinction by illegal collection. This shaded aspect of the succulent trade renders a conservation urgency that the populations of wild *Crassula* must be conserved to ensure that the economic and aesthetic worth of the genus is unbalanced with the requirement of its extended existence [4]. The genus *Crassula* is a versatile species of plants whose history and meaning are much more than meets the eye. Since they first appeared on the rocks of the ancient southern African landscapes to their current ubiquity in living rooms of the world, *Crassula* species have become part of the human culture, medicine and economy. They are living manuals on how to adapt to evolve, showing how strong photosynthesis and plasticity of life forms can create speciation and colonize dry places. They play an important ecological part in their native environments, but their species invasive capabilities elsewhere provide a modern day warning of biological globalization [23]. With the active scientific research still revealing their uncharted biochemical possibilities and conservation efforts still attempting to preserve their wild species, the genus *Crassula* has always been a longstanding study and a source of wonder, a real testament to the strength and adaptability of nature [24].

➢ *Traditional and Ethnomedicinal Uses of Crassula Species*

The genus *Crassula* is a deep and diverse entity in human cultures around the world, not just in terms of its popular use as a robust ornamental, but also in the many layers of traditional medicine, spiritual connotation, and utilization [25]. This strong association of man with these succulent plants is probably best illustrated in their homeland, Africa, where an immense treasure trove of traditional wisdom has long been making use of a broad range of *Crassula* species to treat an enormous array of afflictions. The applications are as manifold as the genus itself, and run the gamut between cures of ordinary digestive ailments and cures of great diseases and even the production of spiritual charms [26].

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Fig 2 Morphological Diversity of Representative *Crassula* Species

The *Crassula ovata*, the common Jade Plant, has been especially extensively documented as a component of the traditional medicine of Africa; historically the Khoikhoi people of South Africa had used it as a medicinal plant to treat gastrointestinal illnesses as well as to disinfect wounds [21]. Moreover, its leaves were boiled in milk and used to treat epilepsy and diarrhea, which emphasizes the strong assimilation of these plants into the local pharmacopoeia. It is not a one-off occurrence and the leaves and leaf juice of other *Crassula* species have been applied topically to treat skin conditions including corns, warts, boils, and inflammation, demonstrating the use of the genus in dermatology [2]. The roots have also been a part of these traditional healing systems, with *Crassula multicava* serving as a strong emetic in traditional medicine, and the roots being used to treat a variety of unspecified remedies. Scientific community has now started to substantiate these ethnobotanical assertions with phytochemical research that has shown that *Crassula* species are good sources of bioactive compounds including phenols, flavonoids and triterpenes that have great antioxidant, antidiabetic and antimicrobial effects. These findings do not just confirm the wisdom of traditional healers but also indicate the possibility of coming up with modern drugs using these traditional remedies [27].

*Crassula* is culturally important not only to Africa, it has been eagerly borrowed and adapted by other cultures, most notably in Asia where it is also known to have numerous symbolic and practical uses in traditional medicine and the ancient art of Feng Shui. Although the jade plant, *Crassula ovata*, is not oriental in nature, it has been so accepted that the plant has become an inseparable part of the image of prosperity and good fortune [28]. The plant is also believed to have medicinal potential in Traditional Chinese Medicine and the folk medicine of the Asian subcontinent more generally, where it is appreciated to a significant aesthetic degree as well. Chinese herbal medicine has incorporated the leaves to treat skin and stomach related diseases with extracts being used to treat wounds, nausea and even diabetes. This agrees with other reports in the area, in which the juice of the leaves was used to treat dysentery with ghee. Its application in Asian folk medicine is incredibly extensive; it has been used to stimulate hematopoiesis (blood cell formation), in oncology, to treat fever and nervous diseases, and has been shown to have perceived systemic effects [29]. The *Crassula* also produced a special ointment which has been used topically to treat joints, speed up wound healing, treat burns and infections, and ease other skin rashes, again demonstrating its potential as a healing agent. But a word of caution soothes this extensive application; folk medicine is aware that the plant harbours minute quantities of arsenic compounds, which makes its use with care and a warning about internal use without expert guidance, a restriction which has so far prevented its acceptance by official medicine. This has not deterred the popular home remedy status of the plant, which practitioners have claimed to be anti-inflammatory, regenerative, antimicrobial, and antiviral [30].

In addition to its medicinal use, *Crassula ovata* has a special role in the Feng Shui, the ancient Chinese philosophical tradition of balancing the human life with the environment. The most well-known "money plant" used in Feng Shui is, perhaps, the Jade Plant, which is known as a universal symbol of bringing wealth, prosperity, and positive energy, or Chi. Its coin-shaped, round leaves are believed to symbolize money and its slow and steady growth is perceived to be a symbol of slow wealth and stability [31]. The exact location of the plant in a home or office is essential to the positive energy of the plant; the southeast corner of a room or building is known as the best place to put a Jade Plant, and the Jade Plant is thought to work better there. Feng Shui also links the earth element with the plant that gives a stabilizing and supportive energy that adds to a stable and harmonious environment. The symbolic power has become so well known that the Jade Plant is a traditional and highly auspicious present to new businesses, housewarmings and any other time that one wishes to send good wishes to prosperity. *Crassula* is also thought to have a Feng Shui effect on other species; such as *Crassula lanuginosa* is also thought to be a wealth magnet, repelling negative energy and bringing financial prosperity, just like the *Crassula* is placed in the southeast

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corner of a room to cause its magic [32]. Feng Shui also has certain numbers of plants that are recommended to enhance various things in life one plant is stability, two is harmony, three is balance in health, wealth and harmony, five is reinforcement of business success, eight to enhance abundance and nine to generate the greatest amount of universal luck. Thus the Jade Plant and its kinsmen have ceased to be botanical specimens and have become participants in the action of creating the energy and good fortune of the spaces in which they are placed, a tribute to the strong cultural resonance of the genus *Crassula* [33].

In addition to their high uses in medicine and spirituality, *Crassula* species have been incorporated into everyday life in numerous other cultural applications, such as as a source of food, as a source of natural dye, and as an insecticide [34]. Although most succulents are poisonous, some species of *Crassula* have been used in cooking, especially in the motherland of South Africa. An example of medicinal-food crossover would be the Khoikhoi people who would boil leaves of *Crassula ovata* or grated roots and drink them with thick milk to treat gastrointestinal problems. Food-wise, the Jade Plant had its leaves grated and cooked to be eaten with milk [35]. According to this tradition, to certain indigenous populations, *Crassula ovata* was not only a medicine, but a part of their diet, with its application having a basis in both nutrition and medicine. Many succulents have a mucilaginous texture, which is appropriate in thickening soups and stews, which might have been applied to these edible *Crassula*. But it is important to observe that there is a very important caution in any reference to the use of *Crassula*. Although used historically, the existence of toxic compounds (such as arsenic) in most species has caused a more current opinion that they should not be consumed casually and instead be used as decorative plants. The fact that poisoning can occur (as diarrhea, vomiting, and weakness) highlights the fact that these historic methods must have been a specialized knowledge, rather than an overall cooking tip [1].

The other interesting use of *Crassula* is that of natural dyes production, a practice which exploits the rich pigmentation and chemical properties of the plant. The name of the species Crassula coccinea is alluding to this relationship, since the suffix coccinea is based on the Greek kokkos, the berry of the scarlet oak that yields a bright red color, and in fact the plant is known to have very bright scarlet flowers. The direct translation of the particular epithet is coloured or dyed scarlet, a direct indication of how the plant was used, or had been used, in historical or perceived application as an agent to give a red hue. In addition to the flowering species, leaves of other Crassula have also been identified as being able to dye [9]. Indicatively, the leaves of *Crassula caffra* are reported to contain large amounts of tannins, which are chemical compounds that are commonly used to create natural dyes, as well as to tan leather. This implies that the plant may be utilized in producing a variety of ground colours and maybe even used as a mordant to stabilise other dyes. In the case of the modern amateur, the Jade Plant (*Crassula ovata*) itself frequently appears as a safe and convenient entry-level option that beginners may wish to consider when first learning about natural dyeing, since it is common, not toxic when used (unlike as an ingestible), and can provide interesting colors. This practical application unites the plant to the ancient traditions, as well as to the modern crafts and practices of sustainable use [21].

Lastly, the genus *Crassula* has taken its niche in pests management as both an insect repelling plant and a target of herbicides owing to its invasive characteristics as well. One of the few distinct and special cases is the South African small succulent *Crassula leachii*. The burning of the plant in its native country is practised, and the resulting smoke emitted is a valuable mosquito repellent, a use of the genus which is novel and an ingenious way of putting it to the service of disease control [7]. This smoke application as opposed to a direct use of plant material is a unique technique in the genus *Crassula*. Moreover, there is a report that Crassula punctata has been employed as a natural insecticide, but no indication of the methods or the insects of interest is given. This indicates a wider, though less reported, possibility that some species might generate compounds that are insecticidal or repellent, a field that should be further scientifically pursued. Similarly, in a sharp and ironic reversal, the roles are reversed as *Crassula* becomes the pest. The invasive *Crassula helmsii* (New Zealand pigmyweed) is so aggressive in many regions of the world particularly Europe that the most potent synthetic herbicides like glyphosate and diquat have been used as the best tools to check its proliferation and reduce its ecological impact. Therefore, the connection between *Crassula* and insecticides is two-fold: humans apply some species to repel the unwanted insects, whereas other species are the victims of herbicidal control as a method of pest control. To sum up, with its use in the savannas of Africa, and in the homes of the Asians, with its medicinal uses, as well as its ornamental qualities, the genus *Crassula* has been a wonderful witness of the many and varied ways in which plants are bound up with human society, to furnish not only beauty, but also food, medicine, and a physical relation to the unseen powers of fortune and well-being [5].

➢ *Phytochemical Composition of Crassula*

The genus *Crassula* is an exceptional source of phytochemical diversity, generating an extensive and intricate repertoire of secondary metabolites, which are gradually becoming the basis of its traditional medical applications and possible contemporary pharmacological purposes. It is no mere academic curiosity to understand the chemical structure of these succulent plants; it is the language in which *Crassula* species communicate with their environment, resist pathogens and manifest their immense biological implications on human health. Phytochemical studies have also shown that *Crassula* species produce compounds of nearly all the major classes of plant secondary metabolites, such as phenolic acids, flavonoids, tannins, triterpenes, sterols, saponins, alkaloids and novel derivatives such as the C-glucoside bergenin mentioned in Table 2 and Fig.3. This chemical complexity is a testament to the long evolutionary history of the genus, and its adaptation to harsh and frequently dry environments, in which these compounds are important in UV protection, herbivore deterrence and resistance to microbial assaults [36].

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Most widely researched and most numerically active group of compounds in *Crassula* are the phenolics and flavonoids, which also are the major contributors to the potent antioxidant, anti-inflammatory, and antimicrobial effects of the genus. The analysis of the Crassulaceae family revealed the isolation of 189 different compounds, of which phenols and flavonoids were the most common. In the case of *Crassula o*vata, a widely used jade plant, phytochemical screening has invariably revealed the existence of phenols, flavonoids and tannins. Studies by high-performance liquid chromatography (HPLC) and liquid chromatography-mass spectrometry (LC-MS) have given a detailed image of these constituents, revealing a group of phenolic acids such as gallic acid, caffeic acid, ferulic acid, chlorogenic acid, p-hydroxybenzoic acid, protocatechuic acid, vanillic acid. The flavonoid profile is also abundant, including such common compounds as quercetin, kaempferol, catechin, apigenin, naringenin, and rutin. One of the most interesting discoveries in one of the studies on *Crassula tetragona* was the significant number of constituents (66) found through HPLC-ESI-MS/MS, the most common phenolic compounds were naringenin, gallic acid and quercetin. The quantitative distribution of these compounds may differ greatly among species with one study showing that the total level of phenolics and flavonoids in leaves of *Crassula sarmentosa* are much greater than in *C. ovata*. This diversity and variability of the phenolic composition is directly related to the high antioxidant properties reported in numerous *Crassula* extracts where phenolics such as quercetin and gallic acid have been shown to be effective free-radical-scavengers [37].

In addition to the simple phenolics, the genus is also a promising source of unique C-glucoside bergenin and its galloyl analogs that have become signature bioactive molecules. Bergenin, gallic acid and kaempferol were first isolated and identified as a large constituent in *C. ovata* that was grown in Iraq. But the most important finding in this course is 11-O-(4'-O-methyl galloyl)-bergenin, which was originally identified as a major constituent in Crassula capitella but later named as one of the major constituents in the *Crassula* cultivar called Himaturi. The compound has aroused considerable pharmacological interest because of its powerful actions; it was observed to suppress platelet aggregation caused by arachidonic acids in a better way than acetylsalicylic acid (aspirin) and possess an anti-oxidative effect equivalent to that of L-ascorbic acid or quercetin. Moreover, this 11-O-(4'-O-methyl galloyl)-bergenin was widely credited with the anti-arthritic effect of *C. capitella* extract in a rat model and was the one that inhibited the course and intensity of rheumatoid arthritis due to antioxidant, anti-inflammatory and membrane-stabilizing actions [38].

Another pillar of *Crassula* phytochemistry is the terpenoid group, which consists of triterpenes and sterols. The content of triterpenoidals was observed to be much higher than that of phenolics and flavonoids in comparative studies of *C. tetragona* and *C. ovata*, highlighting the significance of this group of compounds quantitatively. These species were detected to have 32 hydrocarbon compounds, 7 steroidal components, and 21 fatty acid methyl esters. Another interesting finding of the same research was the discovery and isolation of a new triterpene called 28-Methyl-5alpha-cycloart-12,20, 24- trien-15 alpha -Ol. This mixture of α,b-amyrin had good potential in anti-inflammatory effects by inhibiting cyclooxygenase (COX) enzymes, particularly the COX-2 isoform. These triterpenes and sterols make the genus have a variety of pharmacological profiles such as anti-inflammatory, analgesic and antimicrobial properties [39].

The phytochemical profile of *Crassula* is even more diverse, as it also includes other types of bioactive molecules. Less commonly reported are alkaloids; an example being the isoquinoline alkaloid tetrahydroprotoberberine which was obtained in *C. ovata*. Phytochemical screenings of *C. ovata* leaves have also revealed saponins which possess surfactant and immunomodulatory effects [40]. The hybrid Crassula Buddha Temple offered a rather complicated phytochemical profile, with the presence of not only polyphenols but also sulfur-containing metabolites, tricarboxylic acid cycle intermediates, nucleotides, and compounds resembling peptides. Additional constituents reported in the wider family of Crassulaceae and therefore possibly in *Crassula* contain ascorbic acid (Vitamin C), organic acids, trace elements and the very toxic cardiac glycosides called bufadienolides [41]. The lipid component of *Crassula* species is also chemically complicated with research discovering a variety of fatty acid methyl esters and hydrocarbons such as n-tricontane as a major hydrocarbon constituent. The table below gives a tabular, but not comprehensive, list of the individual chemical compounds which have been detected in different *Crassula* species [42].

Table 2 Chemical Compounds Identified in the Genus *Crassula*

| Compound Name | Chemical Class | *Crassula* Species (Example) |
|---|---|---|
| **Phenolic Acids** | | |
| Caffeic acid | Phenolic acid / Hydroxycinnamic acid | Multiple species |
| Chlorogenic acid | Phenolic acid / Ester of caffeic acid | C. 'Buddha's Temple' |
| Ferulic acid | Phenolic acid / Hydroxycinnamic acid | Multiple species |
| Gallic acid | Phenolic acid / Trihydroxybenzoic acid | *C. ovata*, *C. arborescens*, *C. tetragona* |
| p-Hydroxybenzoic acid | Phenolic acid / Monohydroxybenzoic acid | *C. arborescens* |
| Protocatechuic acid | Phenolic acid / Dihydroxybenzoic acid | *C. arborescens* |
| trans-Cinnamic acid | Phenolic acid / Phenylpropanoid | Multiple species |
| Vanillic acid | Phenolic acid / Dihydroxybenzoic acid | *C. arborescens* |
| **Flavonoids** | | |
| Apigenin | Flavone | Multiple species |

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| | | |
|---|---|---|
| Catechin | Flavan-3-ol | C. 'Buddha's Temple' |
| Isorhamnetin | Flavonol / O-methylated flavonol | C. arborescens |
| Kaempferol | Flavonol | *C. ovata* |
| Lutein | Carotenoid / Xanthophyll (antioxidant) | *C. ovata* |
| Naringenin | Flavanone | Multiple species |
| Quercetin | Flavonol | *C. arborescens*, *C. tetragona* |
| Rutin | Flavonol glycoside | Multiple species |
| **Triterpenes & Sterols** | | |
| α-Amyrin | Pentacyclic triterpene | *C. arborescens* |
| β-Amyrin | Pentacyclic triterpene | *C. arborescens* |
| β-Sitosterol | Phytosterol | *C. arborescens* |
| **C-Glucosides & Derivatives** | | |
| Bergenin | C-glucoside of gallic acid | *C. ovata* |
| **Alkaloids** | | |
| Tetrahydroprotoberberine | Isoquinoline alkaloid | *C. ovata* |
| **Miscellaneous Compounds** | | |
| Ascorbic acid (Vitamin C) | Vitamin / Antioxidant | Reported in Crassulaceae family |
| n-Tricontane | Long-chain alkane (Hydrocarbon) | *C. ovata*, *C. tetragona* |
| Methyl gallate | Phenolic compound (Ester of gallic acid) | *C. arborescens* |

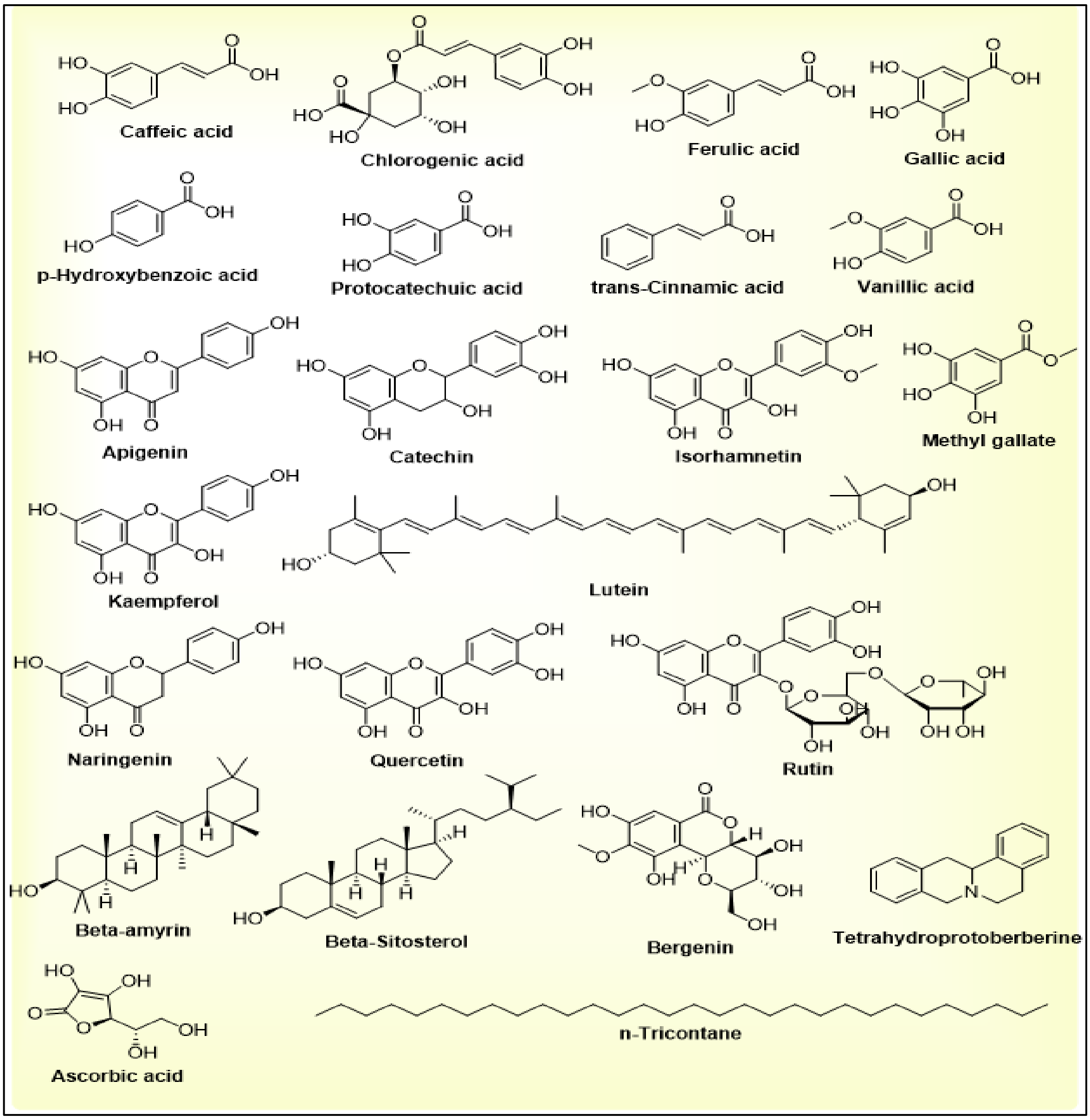

Fig 3 Chemical Compounds Structures Identified in the Genus *Crassula*

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- *Phytochemistry of Crassula ovata*

The lowly Jade Plant (*Crassula ovata*), a staple of sunny windowsills everywhere, is much more than a sign of good luck, and a houseplant that is easy to maintain. Under its shiny, coin-shaped leaves is an advanced and powerful chemical factory, generating an impressive repertoire of secondary metabolites, the real foundation of its impressive resilience and long-standing fame in traditional medicine [43]. The extensive phytochemical profile, which at last started to be carefully studied in the recent decades, is the reason behind the antioxidant, antimicrobial, anti-diabetic, and anti-cancer effects of this plant. With an increased pace in research, *C. ovata* is proving to be an excellent source of bioactive molecules, and there is a great possibility of the discovery of new pharmaceutical agents. The major groups of compounds found are a complex of phenolic compounds and flavonoids, unusual triterpenoids, strong C-glucosides such as bergenin, and the more recent finding of alkaloids, in addition to other basic phytochemicals [25].

The largest and most widely characterized group of compounds in *C. ovata* is the phenolics and flavonoids a family of molecules that iswell-knownas having powerful antioxidant and anti-inflammatory effects [44]. These are the main defense molecules of the plant to oxidative stress due to environmental conditions such as high sunlight and the main source of therapeutic effect of the plant. The presence of these compounds in different extracts of the plant has always been proved by phytochemical screenings. Further sophisticated analytical tools like high-performance liquid chromatography with tandem mass spectrometry have enabled scientists to detect a broad range of specific compounds in these classes Fig.4 and Table 3. A single extensive research discovered 21 various phenolic compounds in *C. ovata*, pointing to the chemical complexity of a single part of a plant. Some of the individual phenolic acids that have been found are gallic acid, caffeic acid, ferulic acid, and chlorogenic acid. The profile of flavonoids is also very heterogeneous, with such commonly and highly bioactive compounds as quercetin, kaempferol, catechin, apigenin, and naringenin. It can be different depending on the geographical origin of the plant, the part of the plant that has been extracted and the solvent applied to extract the compounds. As an example, methanolic extracts tend to be more effective in extracting these polar phenolic compounds as compared to aqueous extracts. It is thought that the synergistic effect of these many phenolic and flavonoid compounds is the cause of the high antioxidant effect seen in *C. ovata* extracts, which have been shown by all conventional tests such as DPPH radical scavenging .

The presence of triterpenoids and steroids is another basis of the phytochemistry of *C. ovata*. Triterpenes are a diverse and large natural product group, frequently linked with anti-inflammatory, antimicrobial and anti-cancer properties. In one of comparative analyses of C. ovata and a close species, *Crassula tetragona*, authors discovered that the triterpenoidal percentage was higher than the phenolic and flavonoid percentage, which shows the quantitative importance of this group of compounds [1]. The content of total triterpenes was measured in the study at 87.06 μg/100μg (ursolic acid equivalent) in *C. ovata*, which was very high compared to *C. tetragona*. This fraction contains a wide variety of molecules, including seven different steroidal components, various hydrocarbons, and n-tricontane is one of the major hydrocarbons. Perhaps most importantly, a new and unprecedented triterpene that had been named 28-Methyl-5alpha-cycloart-12,20,24-trien-15b-Ol was isolated and structurally characterized out of the methylene chloride fraction of *C. ovata* along with five other known compounds. The finding of this new cycloartane-type triterpene also indicates the chemical diversity that is largely unexplored in this ubiquitous houseplant, which may harbor pharmacological properties that have not been studied yet [45].

Arguably the most scientifically fascinating compound to have been studied by scientists in recent years is the bergenin, a striking C-glucoside of gallic acid, which was isolated and identified as a major bioactive constituent of *C. ovata*. Bergenin is a natural product that is relatively rare, and it has a broad spectrum of reported pharmacological activities. Its presence has been associated with high therapeutic effects in *C. ovata* [46]. An innovative study showed how the Jade Plant bergenin extract has a strong synergistic effect when used in combination with the chemotherapy agent, docetaxel, against prostate cells. It was demonstrated that bergenin was capable of causing cell cycle arrest and inducing apoptosis (programmed cell death) in cancer cells, with an $IC_{50}$ of 26, and with the combination of bergenin and docetaxel, the effect of the latter was as potent as a much greater concentration of the former [47]. This result is essential, as it hints that the bergenin may possibly contribute to the minimization of the toxic effects of traditional chemotherapy because it means that smaller, but still effective, doses of therapeutic agents could be used. Bergenin is a prominent C-glucoside which is not the only one in the plant; crassifolioside, an iridoid glycoside has also been detected in the leaves of *C. ovata* further complicating its complicated chemical composition [48].

In one of the most important developments in our knowledge of *C. ovata*, in recent studies the presence of alkaloids, a group of nitrogen-containing compounds commonly linked to strong physiological effects in plants is established. It is an isoquinoline alkaloid which is a group of compounds that has a diverse range of activities, such as possible anti-cancer and neurological actions. The identification of tetrahydroprotoberberine in *C. ovata* sets the stage of absolutely new directions on the research of the pharmacology of the plant since alkaloids are one of the routes to drug development [49]. The plant also has a repertoire of other basic phytochemicals in addition to these more specialized compounds. Saponins, phytosterols, steroids, carbohydrates, and proteins have always been found in phytochemical screenings. Saponins have surfactant and immune-modulating effects, and phytosterols, such as 25-sterols, are structurally equivalent to cholesterol and have been demonstrated to lower cholesterol. The carotenoid lutein, which is a potent antioxidant that is critical in eye health has also been found in the plant [50].

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These compounds are not fixed in their diversity and concentration but can be affected by numerous factors. The selection of extraction solvent is very important because the various solvents will selectively extract various classes of compounds. As an example, methanolic and ethanolic extracts are good in the recovery of phenolics and flavonoids, but the n-hexane fraction has been found to contain some of the lipophilic secondary products such as phytosterols and some triterpenes, and this fraction has been shown to have a good cytotoxic effect on esophageal cancer cells. Moreover, the environmental factors in the environment such as light intensity, water supply and soil composition can radically change production of secondary metabolites in the plant. This is a survival mechanism in the form of metabolic plasticity, which enables the plant to respond to environmental pressures by changing its chemical defense. The table below summarizes the individual chemical compounds that were identified and reported in the scientific literature of *Crassula ovata* [29].

Table 3 Phytochemical Compounds Identified in *Crassula ovata*

| **Chemical Compound** | **Chemical Class** | **Reported Biological Activity / Notes** |
|---|---|---|
| Gallic acid | Phenolic acid | Potent antioxidant, anti-cancer, anti-inflammatory |
| Caffeic acid | Phenolic acid | Antioxidant, anti-inflammatory |
| Ferulic acid | Phenolic acid | Antioxidant, anti-aging |
| Chlorogenic acid | Phenolic acid | Antioxidant, anti-diabetic |
| Quercetin | Flavonol | Potent antioxidant, anti-cancer, anti-inflammatory |
| Kaempferol | Flavonol | Antioxidant, anti-cancer, cardioprotective |
| Catechin | Flavan-3-ol | Antioxidant, cardioprotective |
| Apigenin | Flavone | Anti-inflammatory, anti-cancer |
| Naringenin | Flavanone | Antioxidant, anti-inflammatory, anti-diabetic |
| Lutein | Carotenoid (Xanthophyll) | Antioxidant, essential for eye health |
| β-Sitosterol | Phytosterol | Cholesterol-lowering, anti-inflammatory |
| Bergenin | C-glucoside (of gallic acid) | Anti-cancer (synergistic with docetaxel), anti-arthritic, hepatoprotective |
| Tetrahydroprotoberberine | Isoquinoline alkaloid | Anti-cancer, neuroprotective potential |
| n-Tricontane | Long-chain alkane (Hydrocarbon) | Major hydrocarbon component in lipophilic extracts |

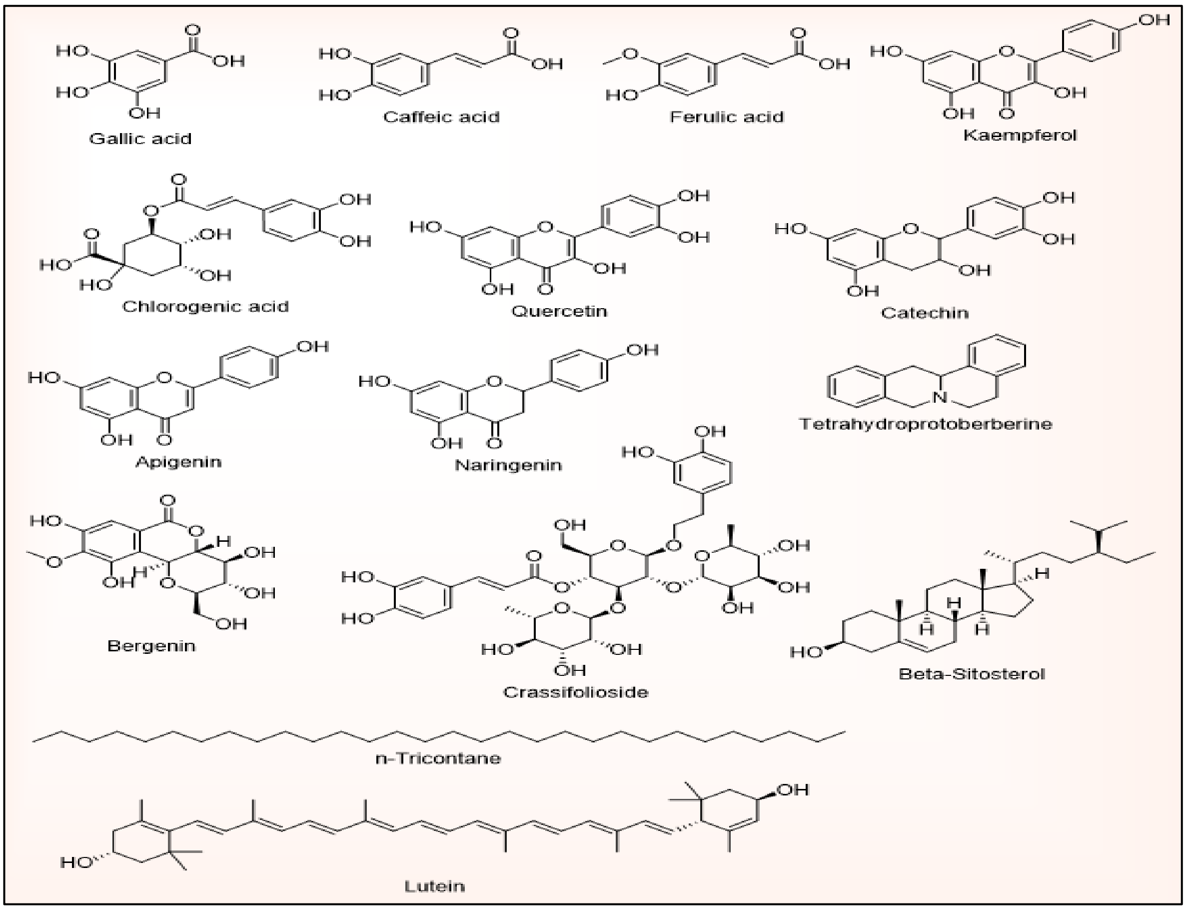


Fig 4 Phytochemistry of *Crassula ovata*

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The phytochemistry of Crassula ovata is an interesting story of a humble ornamental shrub which, in fact, is a very complex manufacturer of bioactive natural products. Its traditional use of quercetin and gallic acid as antioxidants is due to the presence of well-known antioxidants. The identification of a powerful, new triterpene and the great anti-cancer promise of bergenin take the plant out of being a mere folk medicine and give it promising drug leads. The recent discovery of an alkaloid tetrahydroprotoberberine further widens the possible pharmacological perspective of this plant. With more sensitive methods of analysis and more research to be conducted, there is a high possibility that a great number of more unique and therapeutically valuable compounds will be discovered in the unassuming leaves of the Jade Plant, cementing its position not only in our living rooms but also in the future of the pharmaceutical science [37].

➢ *Pharmacological Activity*

*Crassula ovata* has a rich phytochemical composition that directly reflects on the pharmacological activities. The traditional uses of the plant have become scientifically validated by modern scientific studies with a broad range of therapeutic possibilities being actively pursued to develop new pharmaceutical agents.

➢ *Antioxidant Activity*

One of the causal factors of many chronic illnesses, such as cardiovascular diseases, neurodegeneration and cancer, is oxidative stress, an imbalance between the generation of harmful free radicals and the capacity of the body to mitigate them. The antioxidant property of *Crassula ovata* is a basis of defense against this process [51]. *In vitro* researches have shown that the extracts of the plant leaves have strong free-radical-scavenging properties. The property was assessed in one study through the DPPH method, with a maximum inhibition of 85% being obtained with a concentration of 200 μg/ml of a water extract [52]. The ability to achieve this activity can be attributed to the high levels of phenolic compounds and flavonoid, including quercetin and kaempferol, which deactivate reactive oxygen species and inhibit cell damage. The mitigation of oxidative stress by the plant has also been documented in vivo where an extract was reported to decrease malondialdehyde levels, which is an indicator of lipid peroxidation, and at the same time improve the activity of important endogenous antioxidant enzymes such as glutathione, superoxide dismutase, and catalase **Fig.5**. The presence of both free radical scavenging and antioxidant enhancing mechanisms supports the possible use of the plant as a therapeutic agent in the prevention or treatment of oxidative stress-related pathologies [53].

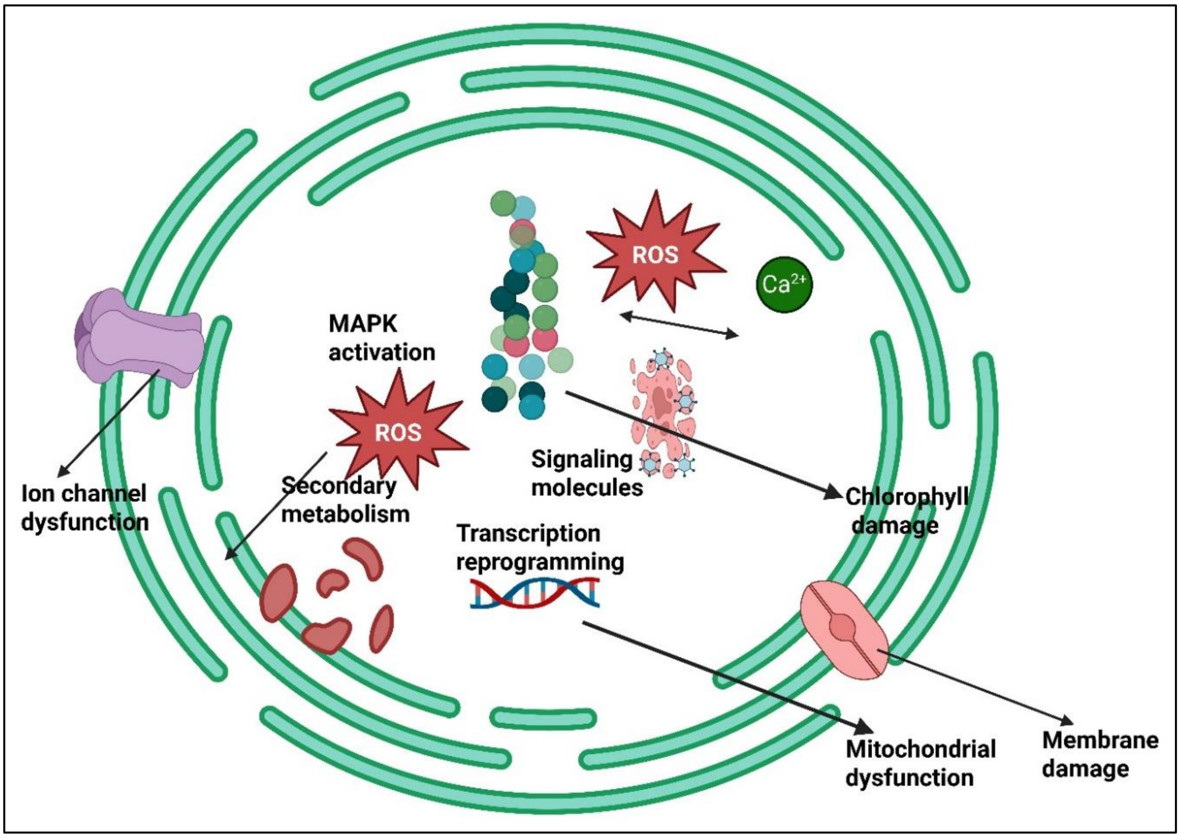


Fig 5 Cellular Responses to Stress Signals

➢ *Antimicrobial Activity*

The use of *Crassula ovata* in traditional medicine for treating wounds and stomach ailments is now supported by compelling evidence of its broad-spectrum antimicrobial activity. It has been scientifically proven that the plant is active against Gram-positive and Gram-negative bacteria, thus making it a prospective source of new antibiotics [54]. It has been found that extracts of *C. ovata* have the capacity of preventing multiplication of various pathogenic bacteria [55, 56]. In one study, there were zones of inhibition with *Escherichia coli* (14 mm), *Proteus vulgaris* (13 mm), Enterobacter cloacae (16 mm), and *Klebsiella pneumoniae*

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(13 mm). It was also active against Gram-positive bacteria, with a significant 22 mm zone of inhibition in the case of *Staphylococcus aureus*. A different study also reported a disc diffusion method as being effective against *E. coli*, *Pseudomonas*, and *Klebsiella sp*. This antimicrobial action is probably because of the existence of phytochemicals like phenols and flavonoids that have the ability to disrupt the cell membranes of bacteria and interfere with key processes of microbes [57]. Such a wide range of activity, in particular against clinically relevant pathogens, would imply that *C. ovata* may be a valuable source of lead compounds to develop novel antimicrobial therapies, particularly in the current period of increased antibiotic resistance [56].

➢ *Antidiabetic Activity*

Diabetes mellitus is a chronic high sugar level in blood that is a health crisis on a global scale. The classical application of *Crassula ovata* in the treatment of diabetes has been strongly supported by the recent pharmacological research that has shown *in vitro* and *in vivo* antidiabetic effects [58]. The main action known is the prevention of an enzyme α-amylase, which breaks down the starches in the diet into simple sugars. A laboratory experiment showed that a methanolic extract of the leaves had the ability to inhibit alpha amylase activity up to 83% at the concentration of 700 µg/ml thus showing its potential of reducing postprandial spikes in blood glucose. This activity was confirmed by further in vivo studies in a streptozotocin (STZ)-induced diabetes rat model [59]. The use of an oral dosage of 200 mg/kg of an ethanolic extract of *C. ovata* was shown to significantly reduce the high levels of blood glucose which are similar to the effects of the standard drug metformin. The extract also had a positive effect on the altered lipid profiles, exhibiting anti-hyperlipidemic effects. These positive impacts are reinforced by the occurrence of bioactive compounds detected using HPLC such as gallic acid, rutin, catechin, kaempferol and quercetin which have been reported to have antidiabetic and antihyperlipidemic effects. The combined findings have placed *C. ovata* as a potential contender in the treatment of diabetes and related metabolic issues [45].

➢ *Anti-Inflammatory Activity*

Inflammation is a multifaceted biological reaction to any harmful stimulus, but when chronic, it is one of the central elements of such diseases like arthritis, asthma, and inflammatory bowel disease [60]. The long history of *Crassula ovata* in African and Chinese traditional medicine includes the use of this plant to treat skin and stomach diseases in both Africa and China, which are caused by inflammation. Modern research that has found the extracts of the plant to have great anti-inflammatory effects supports this traditional knowledge. Although research on *C. ovata* itself is still in its infancy, its significant arsenal of phytochemicals, specifically flavonoids and phenolic acids, is credited with the anti-inflammatory effect. As an example, quercetin and kaempferol, which are found in the plant, have been well reported to inhibit pro-inflammatory mediators like cytokines and enzymes like cyclooxygenase [61]. The triterpenes of the plant, namely α- and β-amyrin are also known to have strong anti-inflammatory properties. The process usually entails countering oxidative stress in that the antioxidant compounds decrease the generation of reactive oxygen species that initiate inflammatory cascades. The bioactive compounds of *C. ovata* can be used in the treatment of inflammatory disorders by reducing the redness, swelling, and pain by reducing oxidative damage and directly blocking the action of inflammatory pathways, which offers a scientific explanation of its historical use in the treatment of inflammatory diseases [62].

➢ *Anticancer Activity*

Perhaps the most promising field of research on *Crassula ovata* is its potential anticancer properties, and studies have shown that it has cytotoxic effects on certain cancer cell lines. The long history of the plant as a treatment of a number of ailments has triggered researchers to study its potential in combating cancer, and in the past few years, there have been major findings [63]. One of the most significant studies assessed the impact of an n-hexane fraction of *C. ovata* on the cells of human esophagus cancer (KYSE-30) [64]. These findings revealed that this fraction had a potent, concentration-dependent anticancer activity. In a related but different study, researchers took a closer look at the compound bergenin, which was derived out of *C. ovata*, and the synergistic action of this compound with the traditional chemotherapy drug, docetaxel, on prostate cancer cells [46]. This combination was discovered to be very effective implying that bergenin may have a potential to increase the effectiveness of the currently used treatments or even enable reduced and less toxic doses of the chemotherapy drugs [47]. Anticancer activity With a number of isolated compounds, such as bergenin, gallic acid, kaempferol, and the alkaloid tetrahydroprotoberberine, this plant is likely to have an anticancer effect [65]. These findings are particularly significant as they highlight *C. ovata* not just as a source of cytotoxic agents but also as a potential source of adjunctive therapies in cancer treatment [19].

➢ *Hepatoprotective Activity*

Liver is a very important organ that is prone to damage due to toxins, medications and diseases resulting in a great burden of hepatic illnesses all over the world. *Crassula ovata* has been tested with regard to its ability to prevent such damage on the liver, termed hepatoprotective activity. The impact of a hydro-alcoholic extract of *C. ovata* on liver-toxic rats with carbon tetrachloride as a hepatotoxin that is also a renowned hepatotoxin was examined in a comprehensive study [66]. The outcomes were very encouraging. The extract significantly improved hepatic functionality as it was able to lower high concentrations of malondialdehyde, a lipid peroxidation and cell damage signaling molecule in the liver. Moreover, it greatly increased the concentrations of important endogenous antioxidants, including glutathione, superoxide dismutase, and catalase and thus reinforced the inherent defense system of the liver to oxidative damage. The extract was also discovered to stimulate hepatic microsomal enzymes, which further helps in the liver detoxification processes. The hepatoprotective effect observed can be driven mostly by the powerful antioxidant properties of the extract which was validated by the presence of various antioxidant compounds including isovitexin, apigenin derivatives and

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quercetin. The results are a solid scientific basis to the traditional application of *C. ovata* in the treatment of liver-related diseases and reasons to highlight its possible use as a natural hepatoprotective agent [26].

- *Wound Healing Activity*

One of the most important aspects of the traditional use of *Crassula ovata* is the promotion of wound healing, which has been used traditionally, especially in the southern part of Africa by the Khoikhoi, who used the plant as a disinfectant to minor cuts and burns, and is still a popular home remedy to minor burns and cuts. Contemporary study is starting to unravel the science behind this effect. The wound healing process is a complicated process that comprises of hemostasis, inflammation, proliferation, and remodeling. A number of these phases are addressed in the properties of *C. ovata* [67]. Its anti-inflammatory and antioxidant properties, which have been well documented, aid in regulating excessive inflammation and alleviating oxidative stress on the wound site, which leads to a more conducive environment in which tissue repair can occur. The strong antimicrobial effect of the plant is also important since the wound infection may slow down the healing process considerably. Moreover, the existence of different phytochemicals such as saponins and flavonoids can trigger the creation of new blood vessels (angiogenesis) and the expansion of fibroblasts, which is necessary to produce the extracellular matrix and seal the wound. Although research is being completed, one of the most recent reviews identifies the wound healing properties of the plant as one of the therapeutic applications of the plant, which justifies its long-time usage in traditional medicine, and also signals its potential development into a contemporary wound care product [68].

- *Toxicity and Safety Profile*

*Crassula* genus has long been praised by its ornamental value and variety of therapeutic possibilities yet a thorough insight into its safety and toxicity profile is also paramount, especially considering how widespread it is in households or how many times it is used in traditional medicine [69]. It is particularly so with the common *Crassula ovata*, the jade plant, whose full safety evaluation cannot be done without a thorough examination of its impact on humans, pets, and its possible therapeutic efficacy. Although it is an incredibly robust and fairly safe plant, it is not totally risk free. The *Crassula ovata* is widely believed to have low toxicity risk to human safety, albeit, not totally harmless. Most sources classify the plant as "mildly poisonous" or having a low level of toxicity [70]. The risks of human contact or ingestion are fairly mild and self-limiting. Ingestion of the plant may cause gastrointestinal upset, and in most reported cases, nausea, vomiting, diarrhea, and abdominal cramps were the most frequently reported. These are most usually the direct response of the body to the irritant compounds of the plant. Fatigue can also be experienced by adults in certain situations. The smaller size of children and babies and the fact they are still developing their systems makes them more susceptible and even minimal amount of the plant may lead to more severe symptoms. In addition to ingestion, the sap of the plant may cause contact dermatitis or rashes, itching, or general discomfort when in contact with skin. It should also be mentioned that these are typically mild and self-limiting symptoms and there is no history of fatal poisoning in humans of *Crassula ovate* [71]. Contrasting the mild effects that have been witnessed in human beings, *Crassula ovata* has been regarded as a serious threat to domestic animals especially dogs and cats. This is a well-known plant that is considered to be poisonous to the two species, with numerous sources estimating it to be moderately-highly poisonous to them. *Crassula ovata* is listed in the ASPCA and other various veterinary sources as a plant that is toxic to cats and dogs, and ingestion may cause a far more severe range of symptoms. Vomiting and diarrhea are the most commonly seen symptoms of pet poisoning. The range of possible symptoms is however more extensive and serious than in humans also encompassing lethargy, depression, lack of appetite and excessive drooling. In more severe instances, pets can develop neurological symptoms, including loss of coordination (ataxia), tremors or weakness. The worst possible outcomes, especially in cats, would consist of the perilously slow heart rate (bradycardia) or other heart rhythm irregularities, which may be fatal unless prompt treatment is given [67]. The precise toxic dose also may depend on the size of the animal and the amount consumed, although because of the possibility of severe complications, it is highly recommended to ensure that these plants are not accessible to pets and that they should be taken to the veterinary as soon as ingestion is suspected. *Crassula ovata* has a paradoxical effect, both as a form of medicine and a possible toxin, making it an essential field of research [72]. The plant has been traditionally used in African traditional medicine to cure various diseases, such as diarrhea, epilepsy, and even as a wound disinfectant. Most of these uses have been confirmed by more recent pharmacological studies which have found potent antioxidant, antimicrobial, anti-inflammatory, and anticancer properties in extracts of it which is credited to an abundance of bioactive compounds such as flavonoids, triterpenes, and alkaloids. The same compounds, which give therapeutic advantages with low, controlled doses, may lead to gastrointestinal distress with higher doses [73].

The absence of standard dosing, the possibility to accumulate some of the compounds over time and the fact that not all of the toxicological profile has been fully studied yet is a strong deterrent against self-medication. Scientific community directly demands an in-depth toxicological analysis prior to the plant being developed into pharmaceutical products in a safe manner. The toxicity of *Crassula ovata* is still under study, yet some important compounds are thought to be the chemical basis of the toxicity. Saponins and alkaloids are the main toxin agents. Saponins are also reported to be gastrointestinal irritants, and this is the reason why vomiting and diarrhea are observed as the most common side effects of ingesting saponins. The fact that alkaloids are present in *C. ovata*, and more so, the recent discovery of tetrahydroprotoberberine-type alkaloid is a highly debated issue, because most alkaloids have strong physiological properties. Moreover, although *C. ovata* itself has not been implicated in cardiac glycoside poisoning, several other genera of the Crassulaceae family, including Kalanchoe, also synthesize bufadienolides that can induce serious heart disease and a long-lasting neurotoxic syndrome

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in animals called krimpsiekte [74]. It can consequently be assumed that *C. ovata* might possess analogous compounds in lower concentrations or that its toxicity profile is due to a synergistic effect of a combination of several chemicals, instead of one toxic compound. Conclusively, even though *Crassula ovata* is a tough and relatively harmless house plant to humans, its relatively slight irritant nature, high level of toxicity in companion animals, and lack of understanding of its long-term medicinal effects all spell a very clear message: it is a plant to admire, not to eat. Responsible use implies keeping it as a decorative, non-edible aspect of the house, far beyond the reach of the inquisitive pets and children [75].

➢ *Future Therapeutic Perspectives and Research Directions*

There is a great potential in the future of therapeutic and research of *Crassula ovata* that promises to be untapped as it seeks to advance beyond the rudimentary characterization to more advanced applications that are more inward looking with regards to the application of modern biotechnology, clinical science and environmental sustainability. One of the fundamental priorities is end-to-end phytochemical profiling by means of sophisticated metabolomics that extends much beyond the classical screening. Nonetheless, an entire untargeted metabolomic strategy is required to chart the entire chemical landscape, discover small or trace bioactive compounds, and develop robust quality control surrogates in future drug formulations. This attempt should be supported by intense in vivo pharmacological validation that has already demonstrated good results: an ethanol extract (200 mg/kg orally) reduced high blood glucose levels and corrected abnormal lipid profiles of streptozotocin-induced Such studies need to be extended to chronic toxicity models, and other disease conditions, including inflammatory disorders and metabolic syndrome. Mechanistic studies are necessary to define the signaling pathways and molecular targets of these effects, based on in vivo efficacy. Although initial studies have determined that the ability of bergenin (isolated *C. ovata*) can result in G0/G1 cell cycle arrest, increase Bax expression and reduce Bcl 2 expression in prostate cancer cells, a lot is still unknown. The future studies must use the method of Western blotting, CRISPR Cas9 gene editing, and pathway specific inhibitors to find out whether the anti inflammatory, anticancer, and neuroprotective effects observed are mediated by NF κB, PI3K/Akt, MAPK or other critical pathways. Rational drug design presupposes such knowledge. Clinical trials and formulation development is the final step in the translational process. Up to now, the majority of the research is preclinical; the subsequent step should involve well designed phase I and phase II trials to determine safety, tolerability and efficacy in humans. At the same time, standardized extracts, nanoformulations, or targeted delivery systems (e.g., liposomes or phytosomes) will need to be developed to improve bioavailability and the reproducible efficacy of such therapies. Biotechnology offers a long-term solution to the harvesting of bioactive compounds in the wild, as biotechnological use of plants will not overexpert the wild plants. Hairy root cultures, developed through *Agrobacterium rhizogenes* mediated transformation, can offer an inexhaustible, scalable source of secondary metabolites as has been shown in many medicinal plants, and this methodology should now be applied to *C. ovata*. Also, the cell suspension cultures and metabolic engineering may be employed to increase the production of high value compounds such as bergenin or the new cycloartan triterpene. The synergistic interaction of *C. ovata* obtained compounds with traditional drugs is another promising area. An earlier landmark study had already demonstrated that bergenin has a good synergistic activity with docetaxel in the case of prostatic cancer cell lines and it has a greater than additive effect.

The application of this paradigm of plant derived molecules as chemosensitizers or adjuvants to reduce toxicity and overcome drug resistance should be investigated in other diseases, including diabetes, epilepsy and infectious diseases. Last but equally important, environmental and biotechnological uses phytoremediation and green roofs are another research direction that is different, yet equally useful. *Crassula ovata* was found to be a possible choice of urban greening, and its low ozone formation potential and its applicability to shallow substrate green roofs. It is already being experimented in areas like Durban, South Africa as a green roof plant since it naturally grows on rocky cliffs. Research in future must measure its ability to take up air pollutants, capture carbon, and its activity in biosorption and phyto-removal of heavy metals or runoff pollution. To summarize, the future research agenda of *Crassula ovata* is quite extensive, and it includes, but is not limited to, deep molecular characterization and clinical translation, sustainable biotechnology, and environmental engineering. By addressing these seven directions in a way that is interdependent, not only will the full therapeutic potential of this iconic succulent be unlocked but it will also be used as a model of how medicinal plants can be used sustainably in the 21st century.

## II. CONCLUSION

*Crassula* is an example of how a collection of simple plants that are commonly dismissed as ornaments may have deep scientific, medicinal and ecological importance. With the ubiquitous jade plant (*Crassula ovata*) on the windowsill to the rare and endemic species of the South African Karoo, these plants have developed an impressive chemical arsenal: phenolics, flavonoids, terpenoids, alkaloids, and novel C-glucosides such as bergenin that forms the basis of their resilience and therapeutic potential. The *Crassula* species have been used traditionally in Africa and Asia to treat gastrointestinal disorders, epilepsy, diabetes, wounds, and inflammation. These uses are now starting to be confirmed by modern pharmacology but they have potent antioxidant, antimicrobial, antidiabetic, anti-inflammatory, anti-convulsant and anti-cancer effects. Of particular interest are the synergistic effect of bergenin of *C. ovata* with docetaxel against prostate cancer, and the hepatoprotective and neuroprotective effects against animal models. Nevertheless, there is a dual-edged safety profile to this promise: it is generally mild in humans, but *Crassula* can induce gastrointestinal upset, and is very toxic to pets, saponins and alkaloids being the probable culprits. In addition, the invasive nature of species such as *C. helmsii* and the risk of poaching of wild populations emphasize the pressing conservation

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issues. Subsequent studies should give emphasis on extensive metabolomic profiling, in-depth studies in vivo and in mechanistic research, clinical trials and biotechnological production of bioactive compounds. Environmental opportunities also exist in sustainably incorporating *Crassula* into green infrastructure and phytoremediation. Finally, the genus *Crassula* is an interesting example of how ethnobotanical wisdom can be translated into evidence-based drug discovery, but requires responsible management of its natural diversity. As the chemistry and pharmacology behind these incredible succulents, they indeed become not just the lowly house plants but also potential sources of future medicines.

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