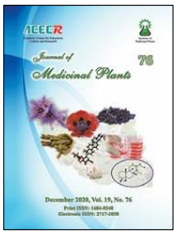
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**Review Article**

# A review of the genus *Caesalpinia* L.: emphasis on the cassane and norcassane compounds and cytotoxicity effects

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Abstract

**Background:** Many herbal remedies have been used in medical systems for the cure of diseases. One of these important applications is usage of them as cytotoxic agents for the treatment of cancers and tumors. Various studies have been conducted on several species of *Caesalpinia* genus including evaluation of antimicrobial, antitumor, anti-inflammatory, antipsoriatic, antidiabetic, antioxidant, antibacterial, immunomodulatory and hypoglycemic activities. Some reports have shown that these plants contain phytochemicals like polyphenols, glycosides, terpenoids, saponins and flavonoids. **Objective:** The aim of this study was to find species of the *Caesalpinia* genus containing diterpene compounds with the structure cassane and norcassane with emphasis on cytotoxic properties. **Methods:** In this study, keywords including *Caesalpinia* genus, cytotoxic and anticancer effects, and cassane and norcassane compounds were searched in Scopus and Science Direct databases. **Results**: Thirteen *Caesalpinia* species were investigated for phytochemical composition and biological effects. Different plant parts of the species including leaves, seeds, stems, roots and legumes contained diterpenes. Among these species, the cytotoxic effects on different cancer cell lines have been evaluated and some had significant cytotoxic effects. **Conclusion:** Present study show that *Caesalpinia* genus has valuable cytotoxic activity but further studies are needed to investigate the active components and their possible development as new anticancer drugs.

## 1. Introduction

Plants have an important role in maintaining health and improving the quality of life for many years. Plants have natural products that can promote health and improve sickness. Today, plant research has increased and many documents have collected to show extensive potential of medicinal plants used in several traditional systems. A great deal of public interest is in the use of herbal remedies. Medicinal plants, derived natural extracts and isolated compounds have many biological

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activities. Cancer disease is the second cause of death all over the world. Cancer was responsible for nearly 9.6 million deaths in 2018. Globally, about 1 in 6 deaths is because of cancer. Approximately 70% of deaths from cancer occur in third world countries. One of the common method for identification of new compounds used in chemotherapy and inhibition cancer process is screening of plants and their second metabolites as cytotoxic agents. For example, several species of Leguminosae and Solanaceae family have been studied for their cytotoxic effects [1 - 6]. One of these plants is *Caesalpinia* genus which have more than 500 species. These species are mostly distributed in tropical or subtropical countries [7]. This genus belongs to Fabaceae (Caesalpiniaceae) family are evergreen trees and shrubs and are cultivated as ornamental plants [8]. These plants are known for their medicinal properties. The generic name regards the botanist, physician and philosopher Andrea Cesalpino (1519-1603) [9].

## 2. Materials and Methods

In this study, keywords including *Caesalpinia* genus, cytotoxic and anticancer effects, and cassane and norcassane compounds were searched in Scopus and Science Direct databases. This review article describes species of the *Caesalpinia* genus that have also been biologically evaluated. On the other hand, the cytotoxicity effects, which is mostly related to cassane and norcassane compounds, have been emphasized.

## 3. Results

In order to classify and present the obtained information, first the botanical description and distribution of the genus, then phytochemistry and different species of the *Caesalpinia* genus were discussed. Finally, the extracted compounds from each species and their structure were presented in the form of tables and figures.

### *3.1. Botany*

#### *3.1.1. Classification of Caesalpinia genus*

Classification of *Caesalpinia* genus has mentioned in Table 1 [10].

**Table 1.** Classification of plant

| **Kingdom** | **Plantae (plants)** |
|---|---|
| Division | Magnoliophyta (Angiosperms) |
| Class | Magnoliopsida (Dicotyledons) |
| Subclass | Rosidae |
| Order | Fabales |
| Family | Caesalpiniaceae |
| Genus | *Caesalpinia* |

#### *3.1.2. Botanical characters of order Fabales*

The Fabales is the order of dicotyledonous flowering plants. This order includes four families and 754 genus that Fabaceae is the main and important family. The obvious specification of this order is the multiplicity seed pod with seeds present in a row. Another specification is root coexistence with nitrogen-fixing bacteria that relief the plants growth on poor soils [11].

#### *3.1.3. Botanical characters of family Caesalpiniaceae*

The plants of Caesalpiniaceae family are perennial or annual, tree, shrub, climbing and very rarely herbaceous. Leaves are alternate and pinnate. Inflorescences are clustered, sideways or terminative. The flowers are bisexual, irregular, with two-way symmetry and often have five fused or free sepals. This plants have four or five sepals (free or contiguous), 5-10 stamens (free or continuously together in different ways), and the upper ovary. Fruits are in the form of pods with seeds that often are without endosperm [12].



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*3.1.4. Botanical characters of genus Caesalpinia*

*Caesalpinia* genus includes trees, shrubs or wooden climbing. Leaves are great and alternate. Stem is straightest, woody or climbing, branched, covered with prickles or without prickles Stipules have lobe or without lobe, by several sizes or without stipules. Calyx is 5 serration. Petals are circular, free, yellow or red. This genus has 5-10 stamens, free or connected, and few ovules. Ovary is without pedicel. Fruit is leathery hard and woody, several shapes, sometimes covered with prickles [13].

*3.2. Distribution*

The genus *Caesalpinia* that consists of an important source of bioactive substances, has more than 500 species. This genus distributed all over the world mainly in tropical or subtropical countries and Namibia and America worm areas. Many of these species are endemic. For example, *C. echinata* exists only in Brazil and *C. pulcherima* is native to Central America and India [7]. *Caesalpinia bond* exists in tropical countries (Pakistan and South & Southeast of Iran) [13].

*3.3. Phytochemistry*

Plants belonging to the genus *Caesalpinia* have been shown to contain different classes of constituents such as polysaccharide, phenolic derivatives, saponins, flavonoids, terpenoids & etc. but the most important compounds are cassane and norcassane diterpenes and cassane furanoditerpenes [14].

The word cassane derived from "Cassa". Cassa is the native name for *Erythrophleum guineense*, the source of a diterpene alkaloid, cassaine. When the biosynthetic rearrangement was occurred in the pimarane precursor, the natural cassane and norcassane diterpenes are produced. They are existed in several genera of Fabaceae family particularly in *Caesalpinia* genus [14].

The basic cassane skeleton is a tricyclic diterpene which has an ethyl group at carbon-13 and a methyl group at carbon-14 position but norcassane has one carbon less from cassane either from carbon-17 or carbon-16 positions (Fig. 1) [14].

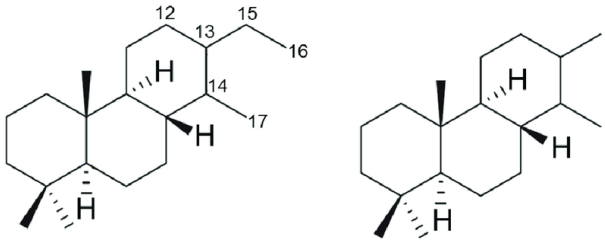



**Fig. 1.** Cassane (left) and norcassane (right) diterpenes skeleton

*3.4. Caesalpinia species*

*3.4.1. Caesalpinia benthamiana* (Baill.) Herend. & Zarucchi

The petroleum extract of *C. benthamiana* root bark was studied and two cassane diterpenoids, benthaminin 1 and 2, and also, a deoxy form of caesaldekarin C (methyl vouacapenate), were isolated, together with *β*-sitosterol and stigmastenone. In this study, the antibacterial and antioxidant effects of *C. benthamiana* are also measured [15].

The name of *Mezoneuron benthamianum* Baill. is a synonym of *Caesalpinia benthamiana* (Baill.) Herend. & Zarucchi. Previous studies on the leaves of this plant showed that methyl gallate and gallic acid are responsible for its antibacterial activity [16].

*3.4.2. Caesalpinia bonduc* (L.) Roxb.

In some references the name *Caesalpinia bonduc* and *Caesalpinia bonducella* are used as synonym [17]. *Caesalpinia crista* "L., p.p.A" is also a synonym of *Caesalpinia bonduc* (L.) Roxb [18]. Caesalls H-M (cassane diterpenoid) were



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isolated from the $CH_2Cl_2$ extract of *C. bonduc* seed kernel. The structures were identified by spectral and chemical methods. These compounds were not cytotoxic against MCF-7, HEP G2 and MG-63 cells [19]. In the other study, caesalls A-F, norcaesalpinin MC, caesalpinin D and bonducellpin were isolated from the ethanol extract of seed kernels of *C. bonduc*. The structures were characterized by NMR and mass spectroscopic data analyses. The cytotoxicity of all compounds were tested against MCF-7, HEP G2 and MG-63 cells. They showed weak inhibitory activities [20].

From the alkaline extract of the endosperm of seeds of *C. bonduc,* a gluco-arabinan was isolated [21]. Methanol extract of *C. bonducella* seed kernel was studied and bonducellpin H, bonducellpin I and 7-acetoxycaesalpinin P (cassane-type furanoditerpenes) were isolated [22].

From the hexane extract of *C. bonduc* plant material, cassane diterpene hemiketals were isolated, caesalpinolide C, caesalpinolide D, caesalpinolide E and cassane furanoditerpene were isolated. The cytotoxicity of these compounds were tested against MCF-7, Du-145, C33A and Vero cell lines. They were shown a low to moderate activity [23].

The investigation on the ethanol extract of *C. bonduc* represented two new homoisoflavonoids, caesalpinianone and 6-O-methylcaesalpinianone with known compounds, stereochenol A, hematoxylol, 4'-O-acetylloganic acid, 6'-O-acetylloganic acid and 2-O-*β*-D-glucosyloxy-4-methoxybenzenepropanoic acid. These compounds were characterized by NMR and mass spectral studies. These compounds were shown glutathione S-transferase (GST) inhibitory and antifungal properties [24].

The leaves methanol extract of *C. bonducella* were studied for antitumor activity against Ehrlich ascites carcinoma (EAC)-bearing Swiss albino mice. The results showed that this extract had remarkable antitumor activity in EAC-bearing mice by decreasing tumor volume, packed cell volume, and viable cell count [25].

Methanol extract of plant materials (legume, seed, aerial part) of *C. bonduc* were prepared and tested through the brine shrimp lethality assay to detect their cytotoxic effects. In comparing, the legume extract of *C. bonduc* showed significant cytotoxicity with $LC_{50}$ value of 25.93 µg/ml [26].

In other researching, the plant materials (legume, seed and aerial part) of *C. bonduc* were extracted with methanol. Extracts were approved for their antiproliferative activity against Du-145 (prostate carcinoma) cancer cell line. Among the tested extracts, legume showed a better activity profile [27].

Another studies have proven antipsoriasis and increasing uterine smooth muscle contraction effects of leaves extract of *C. bonduc* [28, 29]. Antidiabetic and antimicrobial effects are also reported from different extracts of *C. bonducella* seeds [30, 31].

*3.4.3. Caesalpinia decapetala* (Roth) Alston

Decapetpene A, decapetpene B and decapetpene C were isolated from the EtOAc extract of *C. decapetala* seeds. The structure of these substances was identified by spectral data [32].

Two cassane diterpenes (caesaldecapes A&B) were separated from the $CHCl_3$ extract of *C. decapetala* seed by column chromatography and their structures were identified by NMR, MS, and HRESIMS. Caesaldecape A showed cytotoxic activity against KB cancer cell lines. An $IC_{50}$ value was 9.6 µM [33].

From the hexane and ethyl acetate extract of this plant roots, two cassane furanoditerpenoids, caesalacetal and caesalpinetate, and a



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norditerpenoid, caesalpinone were separated. The structures were identified by spectral data. The structure of caesalacetal was confirmed by X-ray crystallographic analysis [34].

*3.4.4. Caesalpinia digyna* Rottler

Bergenin was isolated from *C. digyna* roots and was characterized by its melting point and spectroscopic data. Bergenin exhibits hypolipidemic, antidiabetic and antioxidant activity in type 2 diabetic rats [35].

*3.4.5. Caesalpinia echinata* Lam.

The acetone extract of the stem of *C. echinata* was studied and the echinalides A-G were isolated [36]. Also in further researching, the substances echinalides H-U were isolated and the structures were elucidated by spectroscopic investigation [37]. These compounds showed anti-inflammatory activities [36, 37].

*3.4.6. Caesalpinia ferrea* C.Mart.

From the stems of *C. ferrea*, pauferrol A (a chalcone derivative), was isolated and the structure was determined by NMR spectroscopy. This new chalcone trimmer showed extensive inhibitory activity against human topoisomerase II, and cell proliferation inhibitory activity through the induction of apoptosis in human leukemia HL60 cells with an $IC_{50}$ 5.2 µM [38].

The polysaccharide galactomannan was isolated from the seed of *C. ferrea* and the experiments showed that this substance decreased hyperglycemia in diabetic rats and importantly lowered serum TAG (mediated effects on carbohydrate and lipid metabolism) [39].

Another researching was shown that the aqueous extract of *C. ferrea* stem bark reduced blood glucose levels and improved the metabolic state of the animals (STZ-diabetic rats) [40].

In other works, antiherpes, antitumor and cardiovascular effects of this plant were proved [41-44].

*3.4.7. Caesalpinia gilliesii* (Hook.) D.Dietr.

Hydroalcoholic (70 %) extracts of leaves, flowers and pods of *C. gilliesii* were prepared and their cytotoxicity evaluated against five human tumor cell lines: HEP G2, MCF-7, HCT, HeLa and PC-3. The extract from flowers showed a powerful inhibition of cell growth in several cancer cell lines. A new *β*-sitosterol-3-O-butyl, a known sterol (daucosterol), and two flavonoids (isorhamnetin and isorhamnetin 3-O-rhamnoside) were isolated from dichloromethane fraction of flowers. *β*-Sitosterol-3-O-butyl was the most active compound against both MCF-7 and HEP G2 cells with $IC_{50}$ values of 13.1 and 14.4 µg/ml, respectively [45].

The methanol extract of *C. gilliesii* aerial parts was tested through the brine shrimp lethality assay to detect its cytotoxic effect. It showed cytotoxicity with $LC_{50}$ value of 36.67 µg/ml [2].

*3.4.8. Caesalpinia mimosoides* Lam.

Caesmimosins A-F (cassane diterpenes) were isolated from the fruits of *C. mimosoides*. The structures of these compounds were identified by spectral data. The cytotoxicity of these compounds were studied on human cancer cell lines. They did not show cytotoxic activities at a concentration of 40 µM [46].

The roots of *C. mimosoides* were extracted with $CH_2Cl_2$ and acetone at room temperature. Mimosol A-D (diterpene), mimosol E (dimmer), mimosol F-G (dibenzo [b,d] furans), taepeenin A, taepeenin D, taepeenin L, pterocarpol, bergenin, resveratrol, tetracosyl caffeate were isolated. Several of these compounds were examined for the inhibitory effect on LPS-induced tumor necrosis factor alpha (TNF-α)



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release in RAW264.7 cells. The results showed that mimosol D had extensive inhibitory activity with $IC_{50}$ 6.5 µM [47].

*3.4.9. Caesalpinia minax* Hance

Caesalmin H (cassane furanoditerpenoid), caesalmin B and bonducellpin D (furanoditerpenoid lactones) were isolated from the chloroform fraction of the seeds of *C. minax* and also friedelane triterpenoids, friedelin and epifriedelinol were isolated from the stems of this plant. These structures were identified by spectroscopic methods [48].

Four cassane diterpenes, caesalpines A-D were isolated from the ethyl acetate extract of *C. minax* seed. Their structures were elucidated by NMR and mass spectroscopy [49].

From the EtOAc extract of *C. minax* seed, neocaesalminin A and five furanoditerpenoids, caesalpinin $M_3$, $M_4$, $M_5$, $F_2$ and $F_3$ were isolated. Neocaesalminin A is a furanoditerpenoid with an unusual A-seco-rearranged cassane skeleton. Some of these compounds showed powerful inhibition of nitric oxide production of RAW264.7 macrophages stimulated by lipopolysaccharide (LPS) [50].

The investigations on the $CHCl_3$ extract of *C. minax* seed afforded caesalpinin $M_1$, caesalpinin $M_2$, spirocaesalmin B, caesalmin $E_1$, caesalmin $E_2$, caesalmin $E_3$, caesalpinin $F_1$ (cassane furanoditerpenes). The structures were characterized by the spectroscopic analyses. These compounds showed moderate inhibitory activity on influenza virus neuraminidase (NA) in vitro [51].

Caesalminaxin M and caesalminaxin N were isolated from the $CHCl_3$ extract of *C. minax* seed. Caesalminaxin M was the first example of dicylic cassane-type trinorditerpenoid. The structures were identified by NMR analysis. Caesalminaxin M showed moderate activity against K562 with $IC_{50}$ value of 18.4 µM and Du-145 with $IC_{50}$ value of 35.0 µM [52].

From the EtOAc extract of *C. minax* seeds, cassane diterpenes, sucutiniranes G, H and I were isolated. Structures were identified by different spectral techniques. The cytotoxicity of all compounds were tested against MCF-7 and HEP G2. Sucutiniranes I showed mild antiproliferative activity against MCF-7 with $IC_{50}$ value of 21.4 and HEP G2 with $IC_{50}$ value of 35.6 µg/ml. Sucutiniranes G and H did not show any antiproliferative activity [53].

The seeds of *C. minax* were extracted with methanol. The chloroform fraction was selected to silica gel column chromatography. Two diterpenes, norcaesalpinin I having an unusual ring C-contracted dinorcassane and caesalpinin U having a highly oxygenated furanocassane skeleton were isolated. The cytotoxic activity of these compounds was studied against HEP G2 and HeLa human cancer cell lines. The results showed that norcaesalpinin I had cytotoxic activity against HEP G2 with $IC_{50}$ value of 16.4 µM [54].

From the methanol extract of *C. minax* roots, caesalmins N-Q (cassane diterpenes) were isolated. The cytotoxicity of these compounds were tested against HEP G2, AGS and MCF-7 human cancer cell lines using the MTT method. These compounds was found to show weak cytotoxicity against cancer cell lines [55].

Another researching has investigated the antimalarial effects of diterpene alkaloids isolated from the seeds of *C. minax* [56].

*3.4.10. Caesalpinia platyloba* S.Watson

The dichloromethane extract from the leaves of *C. platyloba* was studied and six cassane diterpenes were isolated. The absolute configurations of all six diterpenes were established by comparison of DFT calculated



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vibrational circular dicroism spectra with those obtained experimentally [57].

*3.4.11. Caesalpinia pulcherrima* (L.) Sw.

The galactomannan from the seeds of *C. pulcherrima* was isolated and purified by ethanol and precipitation method [58].

From the dichloromethane extract of *C. pulcherrima* roots, 15 new cassane diterpenes were isolated. The compounds were named pulcherrins D-R. The structures of these compounds were identified by NMR and mass spectroscopy. Also, the anti-inflammatory activity of these compounds was investigated [59].

From the acetone extract of the aerial parts of *C. pulcherrima*, five flavonoids, 5,7-dimethoxy-3′,4′-methylenedioxyflavanone, *cis*-(Z)-7-hydroxy-3-(4-methoxybenzylidine)-chroman-4-one (isobonducellin), 5,7-dimethoxyflavanone, 2′-hydroxy-2,3,4′,6′-tetramethoxychalcone and the homoisoflavonoid, bonducellin were isolated. The anti-inflammatory activity of isolated compounds was investigated [60].

*3.4.12. Caesalpinia sappan* L.

The EtOAc fraction of heartwood of *C. sappan* was investigated and two new phenolic compounds, (3S,4R)-3,7,2′,3′-tetrahydroxy-3,4-dihydro-9H-indeno[6,5-c] chromene (caesalpiniaphenol E), and (3R,4S)-3,7-dihydroxy-3-(3′-methoxy-4′-hydroxyphenyl)-4-methoxychroman (caesalpiniaphenol F), with brazilin, 3′-O-methyl brazilin, brazilane, 4′-O-methyl brazilin and protosappanin A were isolated. Among these compounds protosappanin A had potent inhibitory activities toward the LPS-induced NO production in macrophage RAW264.7 cells, with $IC_{50}$ 12.5µm [61].

From the seed of *C. sappan*, two new rearranged diterpenoids, tomocinol C and spirocaesalmin C were isolated. Their structures were characterized by spectral data, and their absolute configurations were proved by single crystal X-ray crystallography [62].

Tomocins A-H, phanginin A, phanginin F, phanginin H, phanginin K and neocasalpinin H were isolated from the $CH_2Cl_2$ extract of the seed kernels of *C. sappan* L. [63]. In another work, tomocinon, tomocinol A and tomocinol B (cleistanthane diterpenes) were isolated from the EtOAc extract of the seed of *C. sappan* [64]. Tomocin A, phanginin A, F, H, tomocinon, tomocinol A and tomocinol B showed cytotoxicity against PANC-1 human pancreatic cancer cells [63, 64].

From the methanolic extract of the heartwood of *C. sappan*, a dimeric methanodibenzoxocinone, named neosappanone A, was isolated and its structure was elucidated by spectroscopic analysis. The xanthine oxidase inhibitory activity of this plant from Vietnam to treat gout and related symptoms was investigated [65].

Brazilin was isolated from the EtOAc fraction of *C. sappan* wood. The antiproliferative activity of the methanolic extracts, fractions and isolated compound on HeLa cell line were investigated. Also, the antioxidative activities, total phenolic and flavonoid contents of the methanolic extract and fractions were verified. Brazilin, showed powerful antiproliferative activity with the $IC_{50}$ value of 0.28 µg/ml which was higher than methanolic extract and EtOAc fraction [66].

The ethyl acetate fraction of *C. sappan* heartwood was studied and isoliquiritigenin 2′-methyl ether (ILME) was isolated. The effects of this compound on oral cancer cell lines were investigated by using fluorescence microscopy, MTT assays, Western blotting and flow cytometry. ILME inhibited the growth of the oral cancer cells in a time- and dose-dependent manner. Previously study was reported that a chloroform extract of *C. sappan* L. induces apoptosis in oral cancer cells [67].



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Two new cassane diterpenes, named phanginin L and phanginin M, together with two known furanoditerpenoids, phanginin I and phanginin G were isolated from methanol extract of *C. sappan* seed. The cytotoxicity of these compounds were investigated using SF-268, MCF-7 and HEP G2 cell lines by the MTT assay. Phanginin L showed cytotoxicity against HEP G2 cell line with $IC_{50}$ value of 9.13 µg/ml [68].

The chloroform fraction of the methanolic extract of *C. sappan* seeds was investigated and phanginins N-P (cassane furanoditerpenes) were yielded. All the compounds showed weak cytotoxicity against MCF-7, HEP G2 and HCT-8 cancer cell lines [69].

Two biphenyl dimmers, caesappanin A and B, were isolated from the ethanolic extract of the *C. sappan* heartwood. Caesappanin A showed cytotoxicity against HCT-8, BGC-823, A549 and A2780 with $IC_{50}$ between 1.67 µM and 4.88 µM. [70].

The heartwood of *Lignum Sappan* (*C. sappan*) was extracted with 95% ethanol. Then the ethyl acetate fraction was prepared from methanol extract. Three compounds, sappan chalcone, brazilin and butein were isolated. The influence of the ethyl acetate fraction and its components on growth-related signaling were appraised. The inhibitory effect on the cell cycle was tested by flow cytometric analysis. The results showed that *C. sappan* contains several active compounds with different anticancer activities. The ethyl acetate fraction was better than individual active constituent for the treatment of cancer [71].

From the $CH_2Cl_2$ extract of the *C. sappan* seeds, phanginin A-K were isolated. Phanginin I exhibited cytotoxicity against KB cell line with $IC_{50}$ value of 4.4 µg/ml [72].

11-oxo-Phanginin A, caesalsappanins O-Q and phanginin U were isolated from chloroform extract of *C. sappan* seeds. All the new components exhibited moderate cytotoxicity on MCF-7 (human breast cancer) and HCT-116 (human colon cancer) cell lines [73].

From the *C. sappan* seeds, norcaesalpinin J and phangininoxys B and C (furanoditerpene) were isolated. Norcaesalpinin J has an unusual 20-norcassane hydroperoxide and phangininoxys B and C have cassane hemiketal skeletons. The cytotoxicity of these compounds was investigated against HEP G2, HCT-8 and MCF-7 by MTT method. Norcaesalpinin J showed cytotoxicity against all the tested cell lines, while phangininoxys B and C showed weak activity [74].

From the chloroform extract of the *C. sappan* seeds six new rearranged cassane- type diterpenes named as caesalppans A-F were isolated. The cytotoxic activity of the isolated compounds were tested against cancer cell lines using the MTT method. Caesalppans D showed better cytotoxic activity than others [75].

Two new protosappanins, named caesappin A and B were isolated from the ethyl acetate extract of *C. sappan* heartwood. Caesappin A has a seven-membered ring fusing an acetal-type section. Their cytotoxicity were investigated using MTT assay. Caesappin A showed moderate cytotoxicity against A549 cell line with $IC_{50}$ value of 54.2 µM [76].

Brazilein isolated from the heartwood of *C. sappan*, is a bioactive compounds that shows pharmacological effects such as antimicrobial, anti-oxidative, anti-inflammatory and anti-atherosclerosis properties [77]. In two studies, the anticancer effects of *C. sappan* has been investigated and showed significant effect on the breast cancer cell lines [77, 78].

Also the anti-inflammatory activities of this plant have been studied in other investigations [79-81].



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*3.4.13. Caesalpinia spinosa* (Molina) Kuntze

Six cassane diterpenes, isoneocaesalpin H, caespinosin A-E were isolated from the twigs and leaves of Tara (*C. spinosa*). These cassane diterpenes were firstly reported from Tara. The cytotoxicity of these compounds were studied on HL-60, A-549, SMMC-7721, SW-480 and MCF-7 human cancer cell lines, but they were not active [82].

From the $CHCl_3$ extract of *C. spinosa* (Tara) pods, caesalpinone A was isolated. This compound is a new type of gorgonane sesquiterpenoid which has an unprecedented 1,15-bridge. The structure was identified by NMR spectra. This compound was investigated for the inhibitory activities against five human cancer cell lines but no activity was shown [83].

In other work, the antibacterial and antioxidant effects of *C. spinosa* were investigated [84].

## 4. Discussion

As mention above, the *Caesalpinia* genus had several types of compounds and different pharmacological effects that were shown in Table 2 and 3. Because our emphasis is on the cytotoxicity effects, the compounds that have this effect were shown in Fig. 2.

**Table 2.** The compounds of the *Caesalpinia* species reported in the literature

| Plant | Plant parts | Compound |
|---|---|---|
| *C. benthamiana* | Leaves | Methyl gallate, Gallic acid [16] |
| | Root bark | Benthaminines 1 & 2, Methyl vouacapenate, *β*-Sitosterol, Stigmastenone [15] |
| *C. bonduc* | Seed | Caesalls H-M [19]<br>Caesalls A-F, Caesalpinin D, Bonducellpin D, Norcaesalpinin MC [20]<br>Gluco-arabinan [21]<br>Bonducellpin H&I, 7-Acetoxycaesalpinin P [22] |
| | Bark | Caesalpinianone, 6-O-Methylcaesalpinianone, Hematoxylol, Stereochenol A, 4′-O-Acetylloganic acid, 6′-O-Acetylloganic acid, 2-O-*β*-D-Glucosyloxy-4-methoxybenzenepropanoic acid [24] |
| | Plant material | Caesalpinolides C-E, Friedelin, Lupeol, α & *β*-Amyrin, *β*-Sitosterol, Stigmasterol [23] |
| *C. decapetala* | Seed | Decapetpenes A-C [32]<br>Caesaldecapes A & B [33] |
| | Root | Caesalacetal, Caesalpinetate, Caesalpinone [34] |
| *C. digyna* | Root | Bergenin [35] |
| *C. echinata* | Stem | Echinalides A-G [36]<br>Echinalides H-U [37] |
| *C. ferrea* | Seed | Galactomannan [39] |
| | Stem | Pauferrol A [38] |
| *C. gilliesii* | Flower | *β*-Sitosterol-3-O-butyl, Daucosterol, Isorhamnetin, Isorhamnetin 3-O-rhamnoside [45] |
| *C. mimosoides* | Fruit | Caesmimosins A-F [46] |
| | Root | Mimosols A-G, Taepeenins A, D & L, Nortaepeenin A, Pterocarpol, Bergenin, Resveratrol, Tetracosyl caffeate [47] |



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**Table 2.** The compounds of the *Caesalpinia* species reported in the literature (Continued)

| Plant | Plant parts | Compound |
|---|---|---|
| *C. minax* | Seed | Caesalmins B & H, Bonducellpin D [48]<br>Caesalpines A-D [49]<br>Neocaesalminin A, Caesalpinins $M_3$, $M_4$, $M_5$, $F_2$ & $F_3$ [50]<br>Spirocaesalmin B, Caesalpinins $M_1$ , $M_2$, $E_1$, $E_2$ , $E_3$ & $F_1$ [51]<br>Caesalminaxins M & N [52]<br>Sucutiniranes G, H & I [53]<br>Norcaesalpinin I, Caesalpinin U [54] |
| | Stem | Friedelin, Epifriedelinol [48] |
| | Root | Caesalmins N-Q [55] |
| *C. platyloba* | Leaves | (-)-(5S,6R,8S,9S,10R,14R)-6-Acetoxyvouacapane,<br>(-)-(5S,6R,8S,9S,10R,12Z,14R)-6-Acetoxycassa-12,15-diene,<br>(-)-(5S,6R,8S,9S,10R,13E)-6-Acetoxycassa-13,15-diene,<br>(-)-(5S,6R,8S,9S,10R,14R)-6-Hydroxyvouacapane,<br>(+)-(5S,8S,9S,10R,14R)-6-Oxovouacapane,<br>(+)-(5S,6S,8S,9S,10R,14R)-6-Acetoxyvouacapane [57] |
| *C. pulcherrima* | Seed | Galactomannan [58] |
| | Root | Pulcherrins D-R [59] |
| | Aerial parts | 5,7-Dimethoxy-3′,4′-methylenedioxyflavanone, Isobonducellin,<br>5,7-Dimethoxyflavanone, Bonducellin,<br>2′-Hydroxy-2,3,4′,6′-tetramethoxychalcone [60] |
| *C. sappan* | Seed | Tomocinol C, Spirocaesalmin C [62]<br>Tomocins A-H, Phanginins A, F, H & K, Neocasalpinin H [63]<br>Tomocinon, Tomocinols A & B [64]<br>Phanginins L, M, I & G [68]<br>Phanginins N-P [69]<br>Phanginins A-K [72]<br>11-oxo-Phanginin A, Caesalsappanins O-Q, Phanginin U [73]<br>Norcaesalpinin J, Phangininoxys B&C [74]<br>Caesalppans A-F [75] |
| | Heartwood | Caesalpiniaphenols E & F, Brazilin, 3′-O-Methyl brazilin, Brazilane,<br>4′-O-methyl brazilin, Protosappanin A [61]<br>Neosappanone A [65]<br>Isoliquiritigenin 2′-methyl ether [67]<br>Caesappanin A and B [68, 70]<br>Sappan chalcone, Brazilin, Butein [71]<br>Caesappin A & B [76]<br>Brazilein [77, 78] |
| | Wood | Brazilin [66] |
| *C. spinosa* | Twigs and leaves | Isoneocaesalpin H, Caespinosins A-E [82] |
| | Legume | Caesalpinone A [83] |



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**Table 3.** Pharmacological effects of *Caesalpinia* species

| Plant | Plant parts | Pharmacological effects |
|---|---|---|
| *C. benthamiana* | Leaves | Antibacterial [16] |
| | Root bark | Antioxidant, Antibacterial [15] |
| *C. bonduc* | Seed | Antidiabetic, Antimicrobial [30, 31] |
| | Legume | Cytotoxic [26, 27] |
| | Leaves | Antipsoriasis, Increasing uterine smooth muscle contraction [28, 29] |
| | Bark | Glutathione S-transferase inhibition, Antifungal [24] |
| | Plant material | Cytotoxic [23] |
| *C. decapetala* | Seed | Cytotoxic [33] |
| *C. digyna* | Root | Antidiabetic, Hypolipidemic, Antioxidant [35] |
| *C. echinata* | Stem | Anti-inflammation [36, 37] |
| *C. ferrea* | Seed | Antidiabetic [39]<br>Antiherpes [41]<br>Antitumor [42, 43] |
| | Stem | Cytotoxic [38] |
| | Stem bark | Antidiabetic [40]<br>Cardiovascular [44] |
| *C. gilliesii* | Flowers | Cytotoxic [45] |
| | Aerial parts | Cytotoxic [2] |
| *C. mimosoides* | Root | Inhibitory effect on LPS-induced tumor necrosis factor [47] |
| *C. minax* | Seed | Inhibitory activity on influenza virus neuraminidase (NA) [51]<br>Cytotoxic [52-54]<br>Antimalarial [56] |
| *C. pulcherrima* | Root | Anti-inflammatory [59] |
| | Aerial parts | Anti-inflammatory [60] |
| *C. sappan* | Seed | Cytotoxic [63, 64, 68, 72-75] |
| | Heart wood | Cytotoxic [67, 70, 71, 76, 77]<br>Antimicrobial, Antioxidant, Anti-atherosclerosis [77]<br>Anti-inflammatory [77, 79-81] |
| | Wood | Cytotoxic [66] |
| *C. spinosa* | Legume | Antibacterial[84] |



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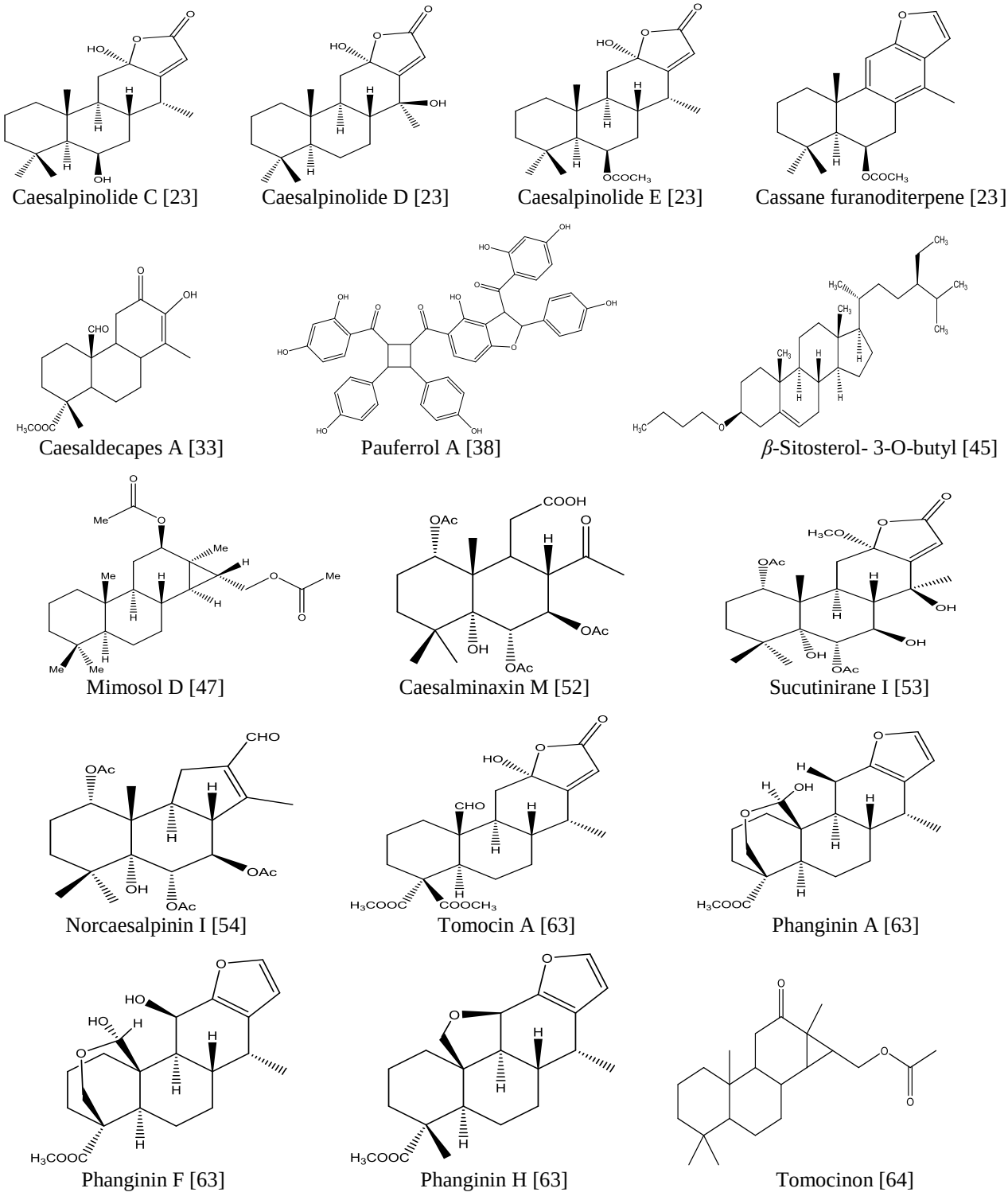



**Fig. 2.** Isolated compounds from *Caesalpinia* species with cytotoxic effects

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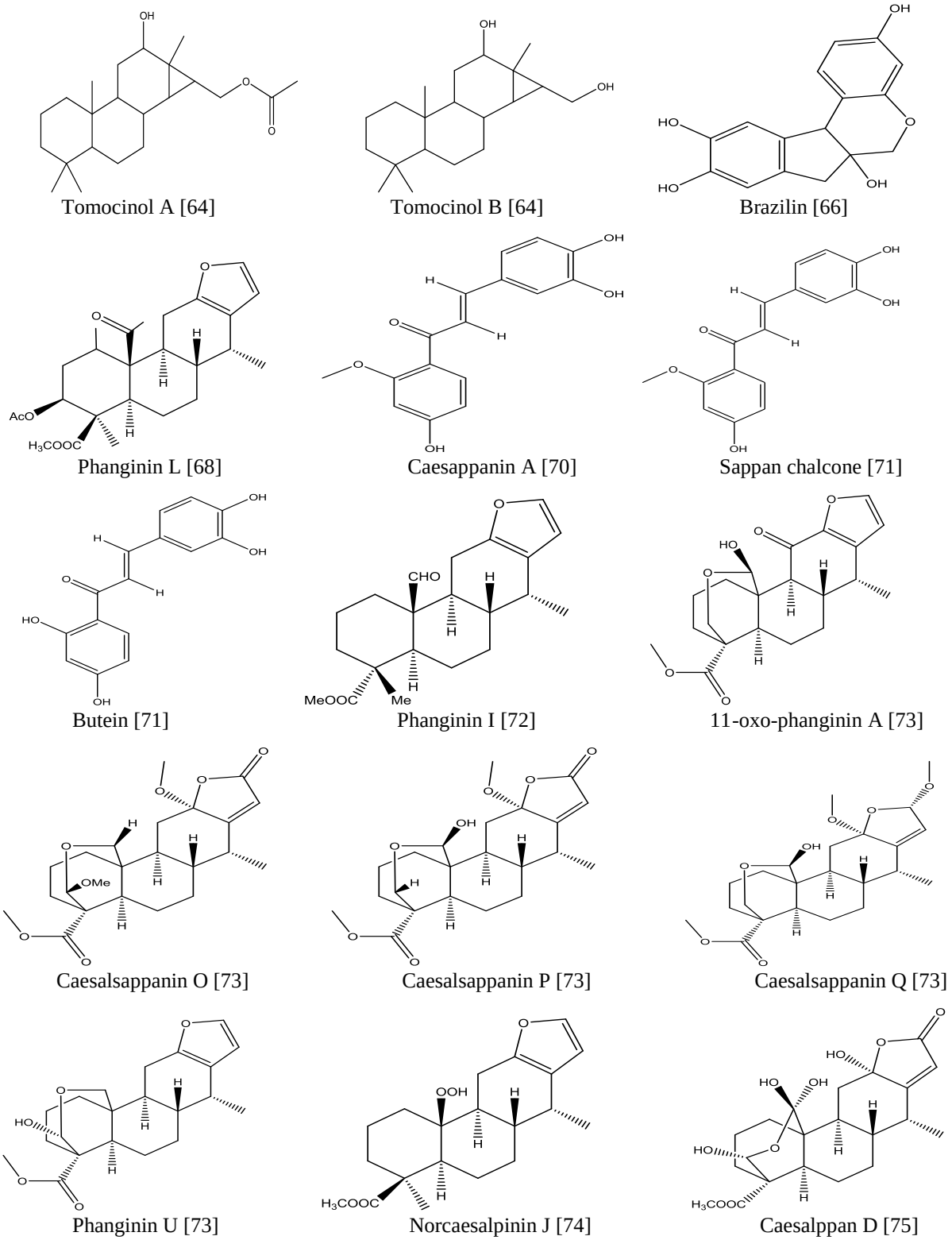
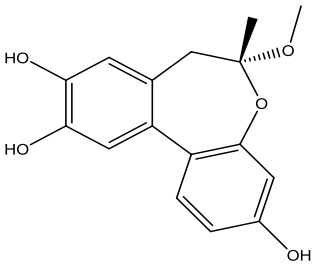


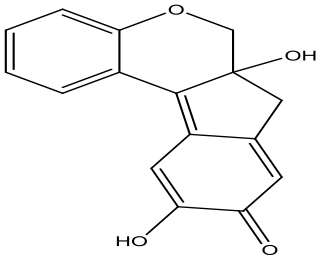

**Fig. 2.** Isolated compounds from *Caesalpinia* species with cytotoxic effects (Continued)



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Caesappin A [76]




Brazilein [77]

**Fig. 2.** Isolated compounds from *Caesalpinia* species with cytotoxic effects (Continued)

## 5. Conclusion

The genus of *Caesalpinia* has more than 500 species. These are mainly distributed in tropical or subtropical countries. This genus belongs to Fabaceae family. They are evergreen trees and shrubs and are cultivated as ornamental plants. The genus of *Caesalpinia* has been shown to contain different classes of constituents such as polysaccharide, phenolic derivatives, saponins, flavonoids, terpenoids but the most important compounds are cassane and norcassane diterpenes and cassane furanoditerpenes. Different plant species of this genus have important pharmacological effects including antioxidant, antibacterial, antifungal, antiviral, antimalarial, antipsoriasis, increasing uterine smooth muscle contraction, antidiabetic, hypolipidemic, anti-inflammatory, antiherpes, cardiovascular effects, and also inhibitory effect on LPS-induced tumor necrosis factor and treat gout. The main biological effects of this genus is cytotoxic and antitumor properties.

In conclusion, the present study provide preliminary data about *Caesalpinia* genus to have cytotoxic activity. Further studies are needed to investigate the active components and their possible development as new anticancer drugs.

## Author contributions

Narges Pournaghi and Farahnaz Khalighi-Sigaroodi collaborated in searching for content, collecting the articles and writing the manuscript. Elahe Safari and Reza Hajiaghaee collaborated in editing the article.

## Conflict of interest

The authors declare that there is no conflict of interest.

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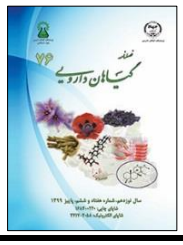
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مقاله مروری

# مروری بر گیاهان جنس ابریشم مصری: با تاکید بر ترکیبات کاسان و نورکاسان و اثرات سمیت سلولی

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**اطلاعات مقاله**

*گل‌واژگان:*
جنس ابریشم مصری
دی‌ترپن‌ها
کاسان
نورکاسان
سمیت سلولی

**چکیده**

**مقدمه:** بسیاری از داروهای گیاهی در سیستم‌های پزشکی برای بهبود بیماری‌ها استفاده شده‌اند. یکی از این کاربردهای مهم، استفاده از آنها به عنوان عوامل سیتوتوکسیک برای درمان سرطان‌ها و تومورها است. مطالعات متعددی بر روی گونه‌های مختلف جنس ابریشم مصری شامل ارزیابی فعالیت‌های ضدمیکروبی، ضدتوموری، ضدالتهابی، ضدپسوریازیس، ضددیابت، آنتی‌اکسیدانی، ضدباکتری، تنظیم‌کننده سیستم ایمنی و کاهش قند خون انجام شده است. برخی گزارش‌ها نشان داده‌اند که این گیاهان حاوی مواد شیمیایی مختلف مانند پلی‌فنول‌ها، گلیکوزیدها، ترپنوئیدها، ساپونین‌ها و فلاونوئیدها می‌باشند. **هدف:** هدف از این مطالعه، یافتن گونه‌هایی از جنس ابریشم مصری حاوی ترکیبات دی‌ترپنی با ساختار کاسان و نورکاسان با تأکید بر خواص سمیت سلولی بود. **روش بررسی:** در این مطالعه، کلمات کلیدی از جمله جنس *Caesalpinia* ، اثرات سیتوتوکسیک و ضد سرطان و ترکیبات cassane و norcassane در پایگاه داده‌های Scopus و Science Direct جستجو شدند. **نتایج:** سیزده گونه ابریشم مصری از نظر ترکیبات فیتوشیمیایی و اثرات بیولوژیکی مورد بررسی قرار گرفت. قسمت‌های مختلف گیاهان از جمله برگ، دانه، ساقه، ریشه و غلاف میوه، حاوی ترکیبات دی‌ترپنی بودند. در میان این گونه‌ها، اثرات سمیت سلولی بر روی رده‌های مختلف سلول سرطانی بررسی شده و برخی از آن‌ها دارای اثرات سیتوتوکسیک قابل توجهی بودند. **نتیجه‌گیری:** مطالعه حاضر نشان می‌دهد که جنس ابریشم مصری، دارای فعالیت سمیت سلولی ارزشمند است، اما برای بررسی اجزای فعال و توسعه احتمالی آنها به عنوان داروهای ضدسرطان جدید، مطالعات بیشتری لازم است.

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