Ethnobotany, phytochemistry, pharmacology and toxicology profiles of *Cassia siamea* Lam.

Mamadou Kamagaté, Camille Koffi*, N’goran Mathieu Kouamé, Aminata Akoubet, N’guessan Alain Roland Yao, Henri Maxime Die-Kakou

**Abstract**

*Cassia siamea* is a shrub belonging to the Fabaceae family, native of Southeast Asia and better known in folklore medicine, feeding, agriculture and manufacture all over the world including Côte d’Ivoire. *C. siamea* has recently been shown to have antimicrobial, antimalarial, antidiabetic, anticancer, hypotensive, diuretic, antioxidant, laxative, anti-inflammatory, analgesic, antipyretic, anxiolytic, antidepressant, and sedative activities. Chromone (anhydrobarakol), Chromone alkaloids (barakol, cassiarin A–B), anthraquinones (chrysophanol, emodin), bianthraquinones (cassiamin A–B), flavonoids and phenolics compounds are the main constituents which are reported in this plant. Barakol was identified as the major constituents of *C. siamea* of leaves and flowers of the world. Due to the easy collection of the plant, widespread and also remarkable biological activities, this plant has become a worldwide medicine. This review presents comprehensive analyzed information on the botanical, chemical, pharmacological and toxicological aspects of *C. siamea*. Web sites of Google Scholar, Pubmed and Hinari were searched for articles published. Some scientific data were collected through Scientific Units of Research and Formation (UFR) of the University Felix Houphouet-Boigny of Abidjan.

**Keywords:** *Cassia siamea* - Ethnobotany - Chemistry – Pharmacology - Toxicology.

**Introduction**

*Cassia siamea* (syn. *Senna siamea*) is an angiosperme native of Southeast Asia (Burma, Ceylon, India, Japan, Malaysia, Sri-Lanka and Thailand) and widely distributed in Africa (Cote d'Ivoire, Eritrea, Ethiopia, Ghana, Kenya, Malaysia, Nigeria, Sierra Leone, South of Africa, Tanzania, Togo, Uganda and Zambia), in Latin America (Cuba, Chile, Antigua and Barbuda, St Lucia, St Vincent and Grenadines and Trinidad and Tobago), and in Oceania (Australia and Fiji). First classified in Caesalpiniaecae family, then in those of *Leguminoseae, C. siamea* is now classified among the *Fabaceae*. This plant is a shrub which has a medium-size, 10-12 m tall, occasionally reaching 20 m. The bole is short; crown dense and rounded at first, later becoming irregular and spreading. The young bark is grey and smooth, and later with longitudinal fissures. The leaves are alternate, 15-30 cm long, compound, with 6-14 leaflets each ending in a tiny bristle. The flowers are bright yellow, in large, up to 60 cm long, upright, with pyramid-shaped panicles. The fruits are flat with indehiscent pod, 5-30 cm long, and constricted between the seeds. There are about 20 seeds per pod. The seeds are bean-shaped, greenish-brown, and 8-15 mm long (Figure 1).
For a long time, *C. siamea* is better known by the tropical populations for its various medicinal virtues.\(^9\)\(^{11}\) It is also known for its various common uses in cattle rearing,\(^12\) agriculture, environment,\(^13\)\(^{14}\) and furniture.\(^15\) Since review and systemic analysis of chemistry, pharmacology and clinical profiles of *C. siamea* have not been reported; we were prompted to provide current available information on traditional and local knowledge, ethnobiological and ethnomedicinal issues, and identification of pharmacologically important molecules, pharmacological and toxicological studies on this useful plant. This review aims at gathering the research work undertaken till to date upon this plant in order to provide sufficient baseline information for future works and commercial exploitation. The scientific information was collected through researcher’s Floristic Center of Abidjan, and Units of Research and Formation (UFR) of Medicine, Pharmacy and Biology of Felix Houphouet Boigny university of Abidjan. Scientific-medical publications were also consulted in different databases (Sciencedirect, Pubmed, and Hinari) using key words such as *Cassia siamea*, *Senna siamea*, *Fabaceae*, *Leguminoseae*, *Caesalpiniaceae*, ethnobotany, chemistry, pharmacology, and toxicology.

**Ethnobotany**

**Vernacular names**

The diverse vernacular names of the plant through the different localities are given in table no. 1

<table>
<thead>
<tr>
<th>Localities</th>
<th>Vernacular names</th>
<th>References</th>
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</thead>
<tbody>
<tr>
<td>Benin</td>
<td>Kassia, cassiatin</td>
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<td>Côte d’Ivoire</td>
<td>Acassia gbéman, acassia oufoué</td>
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<tr>
<td>Ethiopia</td>
<td>Yeferenji digita</td>
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<td>Ghana</td>
<td>Zangara tsi</td>
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<td>Kenya</td>
<td>Ndek obino, Oyieko, Ndege owinu</td>
<td>19, 20</td>
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<tr>
<td>Malaysia</td>
<td>Sebusok, guah Hitam, juah, petai belalang, Johor</td>
<td>22</td>
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<tr>
<td>Nigeria</td>
<td>Bikini raskata, odan</td>
<td></td>
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<tr>
<td>Tanzania, Uganda</td>
<td>Mjohoro</td>
<td></td>
</tr>
<tr>
<td>Togo</td>
<td>Zangalati</td>
<td>24</td>
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<tr>
<td>France</td>
<td>Casse du siam, bois perdrix, de la casse</td>
<td>8</td>
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<td>Creole isles</td>
<td>Kasia</td>
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<td>Spain</td>
<td>Flamboyan Amarillo</td>
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<td>Cambodia</td>
<td>Ángkanh</td>
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<td>India:</td>
<td>Minjiri, manjekonna, kassod, ponavari, vakai, simaiavari, kilek, Nela thangedu</td>
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<td>Indonesia</td>
<td>Bujuk, dulang, johar</td>
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<td>Nepal</td>
<td>Criminal</td>
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<tr>
<td>Philippines</td>
<td>Robles</td>
<td></td>
</tr>
<tr>
<td>Thailand</td>
<td>Kassod tree, yellow cassia, shower thailand, thai pod copper, iron wood, siamese</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>senna, bombay blackwood, black cassia-wood, khilek or khilekluang, khilek-yai,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>chili phak, khi lek ban, sino-Tibet</td>
<td></td>
</tr>
<tr>
<td>Vietnam</td>
<td>Humbo, c [aa] y mu [oo] ng den, mu [oo] ng [egg], mu [oo] ng xi [ee] m</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>muoofng xieem.</td>
<td></td>
</tr>
</tbody>
</table>
**Therapeutic uses**

The leaves, stems, roots, flowers and seeds of *C. siamea* regardless the subspecies have been used for the treatment of several illnesses including mostly malaria, a tropical endemic disease with high morbimortality. In this review, the preparation process of remedies was not clearly described and the dosages prescribed were approximative. Moreover, the treatments are supposed to be continued until recovery. According to the ethnic differences of populations from localities, the plant is used alone or in combination with other plants or with natural substances for the preparation, especially in decoction. For the treatment, people mostly used the preparations by orale administration route.

**Leaves uses**

The leaves are the most used parts’ the plant especially by African and Asian population in preparation of the herbal remedies. In Burkina Faso, fresh and dried leaves decoction (boiled for 20 min in 1L of water) is drunk with lemon juice or for body bath throughout the day to treat malaria and liver disorders. In Côte d’Ivoire, the decoction of leaves is administered orally (0.5 L, twice daily) for treating cough, stomach pains and malaria. Also, in Sierra Leone and Togo, the leaves decoction is drunk against malaria and used as antimicrobial. In Nigeria, the dried leaves are mixed with lemon’s leaves (*Cymbopogon citratus*), pawpaw’s leaves (*Carica papaya*), and the lime’s leaves (*Citrus lemonum*) and are boiled within an hour. The “tea” of the mixture is drunk against malaria. In Uganda, the leaves are picked, cleaned and chewed, and liquid swallowed to treat abdominal pains. In India, the leaves are cleaned thoroughly and boiled. The decoction is filtered in which is added honey. This preparation is drunk ½ glass (150 mL), 3 times a day against anaemia and fever. In Laos, fresh and dried leaves boiled at a ratio of 1:3 for 1 hour 2-3 times to reduce the bitterness, and then crushed to get a paste in which the pork bones are added. This dish called “chi om leck” is taken before breakfast as a vegetable which has sedative and euphorising effects. In Thailand, dried leaves are sprayed to be regularly consumed in capsule form as vegetable for its laxative effect and as sleeping pill. Other authors reported that *Cassia siamea* leaves decoction is drunk against constipation and hypertension and are inhaled in toothache.

**Roots uses**

In Benin, root decoction is used against fever, constipation, hypertension, and insomnia. In Kenya, the infusion, decoction or maceration of mixture of the roots of *C. siamea* and those of *Zanthoxylum chalybeum* are used as antidote for snake bites. In Southeast and Sub-Saharan Africa, and herbalists use the root decoction for the treatment of diabetes mellitus. In these areas, the roots are crushed and mixed then the aqueous extract is drunk to treat sore throat. In Côte d’Ivoire, small repetitive doses of maceration or decoction roots’ bark are drunk to treat angina and malaria, respectively.

**Stems uses**

In Burkina Faso, Ghana and Nigeria, the decoction of the whole stem or stem’s bark is drunk or taken for body bath against malaria and liver disorders. These same uses were reported in Malaysia. Dried stems of *C siamea* mixed with the fruit of *Xylopia aethiopica* is pulverized and administered as laxative. The decoction of the stem bark is drunk against diabetes. This decoction is used as a mild, pleasant, safe, and purgative in Japan. Also, Dalziel (1963) and Keharo (1974) indicated that its decoction is used against scabies, urogenital diseases, herpes, and rhinitis in Cambodia.

**Flowers and seeds uses**

In Burkina Faso, flowers decoction is drunk or used in body bath against malaria and liver disorders. This decoction is also effective against insomnia and asthma.

The seeds are used to charm away intestinal worms and as antidote for snake and scorpion bites. The decoction of the mixture of *C. siamea* and *Ficus thonnigii* fruits’ is drunk to prevent convulsions in children and to treat typhoid fever. In Sri Lanka and Thailand, the flowers and young fruits are regularly consumed as vegetable and for treating curries. It provides laxative and sleeping-aid effect. This dish is also anxiolitic and effective against dysuria.

**Whole plant uses**

The decoction or the maceration of the mixture of different part of *C. siamea* is used for the management of diabetes and used as laxative. In China and Pakistan, the decoction of the leaves and the stems mixture is used as an aperitif, antirheumatic and against swellings.
this decoction is widely used in periodic fever and malaria.\textsuperscript{30}

**Chemistry**

**Qualitative analyse**

Preliminary phytochemical screening of *C. siamea*, showed the presence of chromones and its derivatives (chromone alkaloids, chromones glycosides, dihydronaphthalenone compounds, bischromone), polyphenols (anthraquinones, bianthraquinones, anthrone, flavonoids, isoflavonoids, phenolics, tannins), alkaloids, saponins, steroids, carotenoids, antinutrients (oxalate, phytate), reducing sugars, vitamins, minerals and enzymes.\textsuperscript{31, 49-56} Various bioactive compounds identified from *C. siamea* are shown in Table n°2. The structures of the main constituents are shown in figure n°2.

**Table 2: Chemical composition of *Cassia siamea***

<table>
<thead>
<tr>
<th>Plant part</th>
<th>Extract</th>
<th>Molecular groups</th>
<th>Molecules</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leaves</td>
<td>Chloroform</td>
<td>Chromone alkaloids</td>
<td>Barakol</td>
<td>61, 63, 64</td>
</tr>
<tr>
<td></td>
<td>Methanol</td>
<td>Chromone alkaloids</td>
<td>Anhydrobarakol; 5-acetonyl-7-hydroxy-2-methylchromone; 5-acetonyl-7-hydroxy-5-acetonyl-7-hydroxymethylchromone</td>
<td>59, 60, 121</td>
</tr>
<tr>
<td></td>
<td>Methanol</td>
<td>Chromone alkaloids</td>
<td>cassiarin A, cassiarin B</td>
<td>66, 70</td>
</tr>
<tr>
<td></td>
<td>Methanol</td>
<td>Anthraquinones</td>
<td>Chrysophanol; emodin, physion, rhein, sennosides</td>
<td>3, 121</td>
</tr>
<tr>
<td></td>
<td>Methanol</td>
<td>Bianthraquinones</td>
<td>Cassiamin A, cassiamin B</td>
<td>60, 125</td>
</tr>
<tr>
<td></td>
<td>Methanol</td>
<td>Bischromones</td>
<td>Chrobsiamone A; resins</td>
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<tr>
<td></td>
<td>Ethanol</td>
<td>Triterpenoid</td>
<td>lupeol</td>
<td>58</td>
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<td></td>
<td>Ethanol</td>
<td>Flavonoid</td>
<td>D-pinitol, luteolin</td>
<td>58, 103</td>
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<td></td>
<td>Ethanol</td>
<td>Dihydronaphthalenone</td>
<td>4-(trans)-acetyl-3,6,8-trihydroxy-3-methylidihydronaphthalenone; 4-(cis)-acetyl-3,6,8-trihydroxy-3-methylidihydro-naphthalenone</td>
<td>58</td>
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<tr>
<td></td>
<td>Ethanol</td>
<td>Steroids</td>
<td>β- and γ-sitosterol</td>
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<tr>
<td></td>
<td>Ethanol</td>
<td>Carotenoids</td>
<td>Carotenes, xanthophylls</td>
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<td></td>
<td>Ethanol</td>
<td>Vitamin</td>
<td>Vitamin A,C,E</td>
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<td></td>
<td>Aqueous</td>
<td>isoflavone glycoside</td>
<td>2',4',5,7-tetrahydroxy-8-C-glucosylisoflavone</td>
<td>85</td>
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<td></td>
<td>Hexane</td>
<td>Mineral</td>
<td>Iron , magnesium, manganese, potassium; calcium; sodium; copper; cadmium; lead; phosphorus</td>
<td>49</td>
</tr>
<tr>
<td>Stem bark</td>
<td>Methanol</td>
<td>Bianthraquinones</td>
<td>4'-4(1,3-dihydroxy-2-methyl-6,8-dimethoxy-anthraquinone; 1,1'-bis(4,5-dihydroxy-2-methyl-anthraquinone, cassiamin A, cassiamin B, cassiamin C; madagascar</td>
<td>3, 80, 81</td>
</tr>
<tr>
<td></td>
<td>Methanol</td>
<td>Anthraquinones</td>
<td>Chrysophanol; emodin; physion; chrysophanol-1-O-β-D-glucopyranoside; 1-{[(β-D-glucopyranosyl-(1-6))-O-β-D-glucopyranosyl]-oxy}-8-hydroxy-3-methyl-9,10-anthraquinone; cycloart-25-en-3beta,24-diol</td>
<td>72, 77, 110</td>
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<tr>
<td>Root bark</td>
<td>Methanol</td>
<td>Anthraquinones</td>
<td>Chrysophanol; emodin</td>
<td>76</td>
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<tr>
<td></td>
<td></td>
<td>Bianthraquinones</td>
<td>1,1',3,8,8'-pentahydroxy-3',6-dimethyl[2,2'-bianthracene]</td>
<td>79</td>
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<td></td>
<td></td>
<td></td>
<td>9,9',10,10'-tetrone; 7-chloro-1,1',6,8,8'-pentahydroxy-3,3'-dimethyl[2,2'-bianthracene]-9,9',10,10'-tetrone; cassiamin A, cassiamin B</td>
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<tr>
<td>Flowers</td>
<td>Chloroform</td>
<td>Chromone alkaloids</td>
<td>Barakol ;10, 11-dihydroanhydrobarakol, cassiarin C, D, E, and F</td>
<td>40, 63, 64, 68, 69</td>
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<tr>
<td></td>
<td>Methanol</td>
<td>Chromone alkaloids</td>
<td>Cassiadine</td>
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<tr>
<td></td>
<td></td>
<td>Phenolic acid</td>
<td>Gallic acid; protocatechuic; p-hydroxy benzoic acid; chorogenic acid; Vanilic acid; caffeic acid; syringic acid; p-coumaric acid; ferulic acid; sinapic acid</td>
<td>84</td>
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<tr>
<td></td>
<td></td>
<td>Flavonoid</td>
<td>Rutin; Myricetin; Quercetin; Kaempferol</td>
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<tr>
<td>Seeds</td>
<td>Hexane</td>
<td>Steroids</td>
<td>Cholesterol, stigmasterol, β-sitosterol</td>
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<td>Fatty acid</td>
<td>palmitic, stearic, oleic and linoleic acids</td>
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<td>Aqueous</td>
<td>Anthraquinones</td>
<td>Aloe-emodin, sennosides A₁</td>
<td>74, 75</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vitamin</td>
<td>Vitamin B1, B2, B3, C, E</td>
<td>93</td>
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<tr>
<td></td>
<td>NS</td>
<td>Mineral</td>
<td>Calcium, phosphorus, sodium, magnesium, iron, zinc, copper</td>
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<tr>
<td></td>
<td>NS</td>
<td>amino acids</td>
<td>Lysine, Valine, Leucine, Isoleucine, Threonine, Methionine, Cysteine, Tyrosine, Histidine, Arginine, Aspartic acid, Serine, Glutamic acid, Proline, Glycine, Alanine</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>NS, No specified</td>
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</tbody>
</table>
Cassiarin A
1,1',3,8,8'-pentahydroxy-3',6-dimethoxy-2,2'-bianthracene-9,9',10,10'-tetrone (9)

Cassiarin F
5-chloro-1,1',6,8,8'-pentahydroxy-3,3'-dimethyl-2,2'-bianthracene-9,9,10,10'-tetrone (10)

Cassiarin J
1,1',8,8'-tetrahydroxy-3-hydroxymethyl-6-methyl [2, 2'-bianthracene]-9,9',10,10'-tetrone (11)

Figure 2: Structure of the phytoconstituents of Cassia siamea
Quantitative analysis

The contents of the most bioactive compounds are not known. Quantitative investigations of the leaves, stem bark and seeds of *C. siamea* showed vitamin, amino acid, elemental and proximate contents. Indeed, the oil from its seeds contains a high content of linoleic acid, stigmasterol and β-sitosterol. The main compounds of the essential oils of *C. siamea* are (E)-geranyl acetone (5.8%), 1-octen-3-ol (5.8%),inalool (7.8%),iso-italicene (15.4%) and (E)-β-damascenone (11%). In the seeds, the highest amounts of riboflavin, thiamine, niacin, ascorbic acid andtocopherol (mg/100g) are 0.13, 0.72, 2.08, 8.80 and 3.60, respectively. The elemental contents (mg/100g) of methanol extract / hexane extract of leaves are: Iron 6.74/112, magnesium 126/876, manganese 0.72/35, potassium 257/812; calcium 87.72/932; Sodium 350/612; copper 0.49/0.84; and lead 0.06/0.34, respectively. The elemental contents of methanolic extract of stem bark are: Iron (mg/100g): iron 5.51, magnesium 47.29, manganese 0.88, potassium 116.82, calcium 96.49; sodium 263.16; copper 0.09; nickel 1.05, nickel 3.36, and zinc 17.99. These results justify the traditional use of *C. siamea* in feeding.

Pharmacology

As *C. siamea* is a mixture of various groups of chemicals, it is of no surprise that it exhibits different modes of actions. Its major actions include (i) antimalarial, (ii) anti diabetic, (iii) antitumoral or anticancer, (iv) hypotensive, (v) diuretic, (vi) antioxidant, (vii) laxative, (viii) anti-inflammatory, (ix) analgesic, (x) antipyretic, (xi) anxiolytic, (xii) antidepressant, and (xiii) sedative, and (xiv) antimicrobial activities.

Antimalarial effects

Various extracts of leaves, stem bark, and flowers of *C. siamea* were screened for its antimalarial activity. Most of the activities described were determined in vitro on Plasmodium falciparum strains. Specified and bio-guided fractionation was also based on this antimalarial test. Activities were assessed on different strains, among which are chloroquine sensitive (3D7), chloroquine resistant (W2, FcM29-Cameroon) and multidrug resistant (K1) in order to find effective compounds against resistant malaria. In all studies, alkaloids fraction of the leaves exhibited better anaplasmodial activity than other extracts. This alkaloids fraction, the chloroform and ethanol extracts of the leaves showed activity against 3D7 with IC₅₀ value of 0.24, 2.41 and 7.06 μg/ml, respectively. Cassiarin A is the alkaloid compound which has more potential activities. Its activity is similar to that of chloroquine against 3D7 with IC₅₀ value of 0.005 and 0.006 μg/mL, respectively. The IC₅₀ of this compound was IC₅₀ 0.02 μg/mL against K1. Other compounds isolated from leaves such as cassiarin J (IC₅₀ 0.3 μg/mL), cassiarin K (IC₅₀ 1.4 μg/mL), chrobisiamone A (IC₅₀ 2.6 - 5.6 μg/mL), 5-acetonyl-7-hydroxy-2-methylchromone (IC₅₀ 4.5 - 19.4 μg/mL), anhydrobarakol (IC₅₀ 7.8 μg/mL), cassiarin B (IC₅₀ 22 μg/mL), cassiarin G (IC₅₀ > 50 μg/mL), and cassiarin H (IC₅₀ >50 μg/mL) showed moderate activity against 3D7, respectively. Tested on W2, the chloroform, methanol, and hydroalcoholic extract of this plant part showed moderate activity with IC₅₀ similar value up to 10 μg/mL; while the aqueous extract showed the lowest activity with IC₅₀ value of 23.15 μg/mL.

Among stem bark extracts, chloroform extract (IC₅₀ 21±3 μg/mL) was the most interesting with promising antimalarial activity followed by ethanol extract (IC₅₀ 31±5 μg/mL) and aqueous extract (IC₅₀ > 100 μg/mL) on FcM2930. Against K1, Etyl acetate fraction of this part plant was active with IC₅₀ 31±3 μg/mL and this activity was associated to emodin and lupeol which displayed similar IC₅₀ value of 5 μg/mL.

Phytochemical investigation of the flowers also afforded cassiarin C and 10,11-dihydroxyhydrobarakol which possessed weak antiplasmodial activity with IC₅₀ value of 24.2 μg/mL and 5.6 μg/mL against 3D7, respectively.

Three others alkaloids isolated from the flowers such as cassiarin D, E, and F with potent antimalarial activity were reported.

These in vitro studies were confirmed by in vivo studies. Indeed, the oral administration of *C. siamea*’s aqueous extract of leaves including alkaloids and quinines reduced parasitemia and hyperthermia in patients, significantly.
In addition, the effectiveness of *C. siamea* leaves’ aqueous extract on mosquitos larvae was investigated against *Aedes aegypti* by determining the median lethal concentration (LC$_{50}$) within 24, 48, 72, and 96 hours. The results indicated that this extract exhibited 50 % inhibition of mosquito larvae at 419.65 mg/mL for 24 hours and at 218.43 mg/mL for 96 hours, respectively. Also, in chronic administration within 21 days, chloroform extract of the stem bark including coumarin and betulinic exhibit 100 % and 90% of mortality on *Aedes aegypti*. So, *C. siamea* could be used effectively as indigenous mosquito control agents alternatively to conventional chemical mosquitos.

### Antidiabetic and anti-lipemic effects

The potential effects of *C. siamea* (leaves, roots) on endocrinological system were evaluated by several methods. Ethanolic, ethyl acetate and hexane extracts of *C. siamea*’s leaves at doses 150 and 300 mg/kg were tested for antidiabetic activity in alloxan induced diabetes model and the plasma blood glucose levels were estimated by GOD-POD method at 0, 2, 4, 6, 8 and 12 hr. So, ethyl acetate extract of *C. siamea*’s leaves at both different doses produced significant reduction when compared to ethanol and hexane extracts (P<0.001). Ethanolic extract of leaves of *C. siamea* exhibits a hypoglycemic and antihyperglycemic effect in non-diabetic rats after induction of hyperglycemia with 2 g/kg/bw of glucose feeding within 1-5 hours. Indeed, this extract administrated orally at the doses of 500 and 750 mg/kg/bw significantly decreased blood glucose by 50.32 and 47.29 % per hour with glibencamide (10 mg/kg/bw) as positive control (P<0.05). The aqueous extract of *C. siamea*’s root (1000 -3000 mg/kg, orally) caused improvement blood glucose level and body weights within 24 hours in alloxan-induced hyperglycemic rats, significantly (P< 0.05). We reported that sun-dried and freshly uprooted root have the same antidiabetic potential. In addition, administrations of leaves’ methanolic extract (250, 500 mg/kg, orally) within three week induced a significant decrease in streptozotocin (STZ) diabetic rats with high blood glucose levels. It also reduced their serum cholesterol and triglycerides and improved their HDL-cholesterol level (P<0.01). Bioassay guided fractionation of the ethyl-acetate extract of *C. siamea* afforded 6 known compounds such as chrysophanol, physcion, emodin, cassiamin A, friedelin and cycloart-25-en-3β-24-diol. These compounds were further evaluated for pancreatic lipase inhibitory activity. Cassiamin A was found to be most active with IC$_{50}$ value of 41.8 μM. Physcion and friedelin were found to be moderate enzyme inhibitors. The results indicate the antihyperglycemic potential of *C. siamea* roots through pancreatic lipase inhibition. Barakol seems to have no antidiabetic effects. Overall, the results demonstrate significant antihyperglycemic, antidiabetic and anti-lipemic activities of *C. siamea* and justify the use of this plant in the treatment of diabetes. However, further investigations are therefore needed to go thoroughly into the molecular mechanisms and identify other bioactive molecules responsible for antidiabetic activity.

### Antioxidant effects

An antioxidant is defined as any substance that when present at low concentrations compared to those of an oxidizable substrate, significantly delays or prevents oxidation of that substrate. In this review, in vitro studies showed that various extracts of *C. siamea* possessed high antioxidant potential measuring using β-carotene bleaching method, 2,2’-azinobis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) radical cation and superoxide anion radical scavenging assay. Indeed, methanol and aqueous extract of barks (800 and 1000 μg/mL) inhibited 60.5% and 51.34% free radicals compared to those of rutin which exhibited 62.56% inhibition, respectively. While at 1000 μg/mL hexane, chloroform and ethyl acetate extracts of leaves showed moderate antioxidant activities, respectively.

DPPH radical scavenging activity of flowers has been done. The results showed that the methanolic extract of flowers (250 μg/ml) neutralized 96% of DPPH radicles. This extract (500 μg/ml) scavenged 42.7%, 32.7% and 64.5% of the O$_2$•-, H$_2$O$_2$• and NO, respectively. Also, methanol extract of leaves reduced hydroxyl radicals (OH•), peroxyl (ROO•) and superoxide (O$_2$•-) with IC$_{50}$ value of 349.9 μg extract/mg DPPH.

In vivo, ethanol extract of flowers (50-150 mg/kg; p.o) significantly protected against acute phase of hepatotoxicity and histopathological changes (necrosis, fatty degeneration) induced by a single intraperitoneal injection of carbon tetrachloride (CCl$_4$) in male Wistar rats. These results showed that *C. siamea* could afford significantly protection against oxidative damages to major biomolecules in the liver.

Many antioxidant compounds such as barakol, vitamin C, Vitamin E, carotenoids, α-tocopherol, xanthophylls, tannins, flavonoid, phénolic acids, and diverse enzymes...
(superoxide dismutase, catalase, and peroxidase) could be responsible for this activity. So, barakol scavenged the DPPH radical 1.3 times higher than those of butylate hydroxytoluen (BHT) with EC_{50} value of 9.18 mg/mL. Mechanisms of action of some of these identified natural antioxidants are known.

**Antitumor or anticancer effects**

In research of natural or synthetic products as cancer chemopreventive agents, in vivo and in vitro antitumor activity studies were conducted with various extract of leaves and stem bark of *C. siamea*. In male wistar rats, feeding diet containing 4-5% of leaves of *C. siamea* for 2 weeks significantly reduced the activities of some hepatic P450 dependent monoxygenases such as aniline hydroxylase (ANH) and aminopyrine-N-demethylease (AMD) as well as the capacity to activate the mutagenicity of AFB1 towards Salmonella typhimurium TA100 is 31.73 % and 41 %. It increased the activities of glutathione S-transferase (GST) for 250% and UDP-glucurononyltransferase (UGT) for 220% which are phase II detoxification enzymes. It also decreased the multiplicity of mammary gland tumors as well as it slight delay of the onset of tumor development in female Sprague Dawley rats treated with carcinogenic agent such as 7,12-dimethylbenz[a]anthracene (DMBA). This activity may be partly due to its phase II enzyme inducing capacity as well as its phase I enzyme inhibitory ability in rat liver. In addition; dietary *C. siamea*’s leaves did not induce micronucleus formation in mouse peripheral blood reticulocytes. Furthermore, it showed anticlastogenic potential against DMBA and cyclophosphamide-induced reticulocyte micronucleus formation.

**In vitro**, clinical trials demonstrated that the plant aqueous extracts inhibited human recombinant hepatic cytochrome P450 such as CYP_{3}C_{9} and GSTM1-1 with IC_{50} value of 346.5 mg/ml and 50 mg/ml, respectively. This inhibition of GSTs may be beneficial for cancer therapy. Also, petroleum ether, dichloromethane, ethanol and aqueous extracts of leaf showed cytotoxicity against human epidermoid carcinoma (KB) cell lines with IC_{50} value between 67 and 100 μg/ml. However, methanol extract of leaves was inactive on human oral epidermal carcinoma (KB), breast adenocarcinoma (MCF-7) and small cell lung carcinoma’s (NCI-H187) proliferation.

The anticancer properties of *C. siamea* could be due to anthraquinones (emodin and its derivatives) and bianthaquinones (cassiamin B and its derivatives). Indeed, twelve of these compounds have been tested for their inhibitory activities on EBV-EA activation induced by 12-O-tetradecanoylphorbol-13-acetate (TPA) in Raji cells using a short-term assay. Then, inhibitory effects of emodin and cassiamin B on mouse two-stage skin carcinogenesis model using DMBA or NOR-1 as an initiator and TPA as a promoter were performed by skin rubbing. All the results indicated that anthraquinone monomers showed higher anticancer activity than bianthaquinones. The effects of these anti-tumor promoters’ molecules were correlated to their standard redox potentials and their electronic properties using PM3 method with CAChe MOPAC program.

**Antihypertensive effects**

Studies on antihypertensive activities of *C. siamea* (leaves) was undertaken to find the pharmacological basis for the ethnomedical use of the plant. In vitro, chloroform and methanol extract of leaves showed promising dose-dependent vasorelaxant action by measurement of vascular isometric force in endothelium-intact and -denuded mesenteric artery rings. Two chromones alkaloids like cassiarin A and barakol were responsible for this activity. Indeed, acute pre-treatment with barakol (10 mg/kg, iv) reduced the beating heart rate for 89% with significant fall of the systemic blood pressure in anesthetized rats for 86%128. Barakol also showed significant protective effects on aconitine-induced ventricular fibrillation and tachycardia in cats and rats. In contrast, vasorelaxant action of barakol was attenuated by its chronic administration (p<0.05). The mechanisms of action of antihypertensive compounds were unclear and needed further investigations. Nevertheless, preclinical assay showed that cassiarin A vasorelaxant effect in wistar rats was partially mediated by endothelium-derived releasing factor (EDRF), nitric oxide (NO) and prostaglacycline (PGI2).

**Laxative effects**

*C. siamea* (leaves, flowers) is known for its laxative effect in Thailand. Several laxative compounds such as anhydrobarakol, barakol, aloe-emodin, rhein-8-monogluicoside, rhein, chrysophanic acid, anthrone, dianthrone, chrysophanol, sennoside A were identified in this plant. For example, sennoside A of *C. siamea* (20-30 mg/kg, po) in combination with other compounds (guanethidine, neostigmine, castor oil and intraluminal hypertonic glucose) induced a strong myoelectric inhibition of the colon about 10 hours after administration.
which was followed by an abundant diarrhea in dog. Barakol caused laxative effect on small intestine and colon via excitation of cholinergic motor neurons with EC_{50} 0.3 and 0.4 mM, respectively. In this activity, barakol stimulated chloride secretion without affecting electrogenic sodium absorption in rat colonic epithelium. The mechanisms involved basolateral Na^{+}+K^{+}-2Cl^{-} cotransporters and apical Cl- channels which were partly mediated by the release of cyclooxygenase metabolites. These results indicated that barakol and sennosides may produce a purgative action in small intestine which may be clinically important in patients with intestinal hypomotility disorders.

Anti-inflammatory, analgesic and antipyretic effects

Nsonde-Ntandou et al., (2010) have shown that ethanol and aqueous extracts of C. siamea’s leaves and stem bark (100 – 400 mg/kg, po, for 4 hours) had significant dose-dependent anti-inflammatory, analgesic and antipyretic activities using experimental rat models (p<0.01). The results indicate that aqueous extracts had better anti-inflammatory potential than diclofenac (5 mg/kg, po) on paw oedema using hot plate test. The mechanisms of action involved inhibition of cyclooxygenase. The analgesic and antipyretic effects of these extracts were more important than paracetamol (50 mg/kg, po) and morphine (2 mg/kg, po) (p <0.001). Recently, Monin et al. (2012) have been shown that leaves’ ethanol extract exhibited high analgesic activity using acetic acid induced writhing test in mice. They found that leaves’ ethanol extract (500 mg/kg) exhibit significant inhibition of writhing reflex by 61.98% while the diclofenac (25 mg/kg) Na inhibition was found to be 85.95% (p<0.001). These results justify the traditional use of C. siamea in fever. However, the bioactive compounds of C. siamea responsible to these activities were not specified. According to the literature, four major families of compounds may explain these activities: triterpenes (lupeol, oleanolic acid, ursolic acid, friedelin, and betulin), flavonoids (apigenin, kaempferol, and luteolin), anthraquinones (emodin), phytosterols (stigmasterol, β-sitosterol).

Anxiolytic, antidepressant and sedative effects

C. siamea (leaves, flowers) is active on central nervous system. Anxiolytic effect of aqueous extracts of leaves and flowers (10 - 120 mg/kg, po) were demonstrated using an elevated plus-maze (EPM) test in rats. Also, clinical trials reported that leaves’ alcoholic extracts used as syrup or tablet (10 mg/kg, po) caused drowsiness and improve sleep quality in insomniac patients. Barakol was the only compound identified in these neuropharmacological activities. Indeed, barakol (10 mg/kg; ip) showed similar anxiolitic activity as diazepam (1 mg/kg, ip) in wistar rats. But, it increased locomotor behavior contrary to diazepam. The mechanism of action involved inhibition of endogenous dopamine (DA) release and turnover in the rat striatum. This inhibition was antagonized by the dopamine D2 receptor antagonist eticlopride, suggesting that the anti-anxiety activity of barakol may be related to its agonistic activity without a change in dopamine uptake. However, the lowest dose of barakol showed no effect on exploratory behaviours using the holeboard test which indicates that 5HT mechanism and 5HT_{1A} receptor may not be involved in the anxiolytic effects. Then, barakol (10 - 100 mg/kg, p.o.) had no anxiolytic effects in male wistar rats using an EPM test. These constrast results suggest that anxiolitic effect of barakol was dose-dependent and required a peritoneal administration.

The antidepressant effect of barakol (5 - 30 mg/kg, po, for 7 days) was similar to that of imipramine (25 mg/kg, po). Also, barakol (5 - 25 mg/kg, ip) decreased the duration of immobility and increased struggling in isolated and stressed rats using the forced swimming test (P<0.05). In contrast, barakol (5 - 10 mg/kg ip) had not antidepressant effect in the socially reared rats. So, we must pay attention to experimental conditions because socially conditions of animal influence the antidepressive effect of C. siamea.

The sedative effect of barakol was assessed in mice behaviour using neurochemical tests. So, chronic administration of barakol (10 - 100 mg/kg, po; for 30 days.) reduced spontaneous locomotor activity, increased the duration of sleeping and prolonged the thioipental-induced sleeping duration in wistar rats. Its sedative effect does not involve the GABA or glycine systems but may be via the chloride ion channel like barbiturates. Thus, these studies suggest that the acute barakol administration by intraperitoneal route exerts an anxiolytic effect while the long-term treatment by oral administration causes sedation. Therefore, it is essential to consider carefully when assessing the value of barakol as anxiolytic or sedative drugs.

Antibacterial effects
C. siamea (leave) has been valued for its use in the treatment of infectious diseases. Recently, interest in C. siamea has focused on its antibacterial activity evaluated against various Gram positive and Gram negative bacteria species by using cylinder plate assay.\textsuperscript{151}

The methanol leave extract showed strong antibacterial activity against Bacillus cereus and Listeria monocytogenes with IC\textsubscript{50} 5.2 mg/mL and 20.8 mg/mL for 24 hours exposition at 37°C, respectively. In the same conditions, it had low activity against Escherichia coli, Klebsiella pneumoniae, Pseudomonas fluorescens, Salmonella rissen, Salmonella typhimurium, Staphilococcus aureus, Yersinia enterocolitica, Lactobacillus planetarium with IC\textsubscript{50} up to 166.7 mg/mL.\textsuperscript{115} At 400 μg/disc hexane extract showed high activities on Corynebacterium diphtheriae, Salmonella typhi, Shigella sonii, Pseudomonas aeruginosa, Shigella boydii at 37°C within 24 hours but it inactive on Proteus mirabilis, Staphylococcus aureus and Staphylococcus pyogenes. Alkaloids, phenolics and sterols could be responsible to this effects.\textsuperscript{152}

The ethanol leave extract (500 - 1000 μg/disc) showed more activities than ciprofloxacin (30μg/disc) on Staphylococcus aureus.\textsuperscript{59} It showed moderate activity on Bacillus subtilis but it inactive on Escherichia coli and Pseudomonas aeruginosa. At 40 mg/mL concentration for 18 hours exposition, it showed highest activity on Salmonella thyphi with inhibition zone (iz.) value of 10 mm followed acetone and aqueous extracts with iz. 15, 8 and 3.5 mm, respectively. These effects were compared to those of ampicillin, chloramphenicol, cotrimoxazole and ciprofloxacin at 5 mg/mL which showed inhibition zone value of 8, 16, 14, and 30 mm, respectively.\textsuperscript{153}

Aqueous leave extract is active against various bacteria Gram-. At 500 and 1000 μg/mL/disc, it inhibited Pseudomonas aeruginosa (iz. 16 mm, respectively). At 0.1mL/disc/37°C for 24 hours, it showed inhibition on Staphylococcus aureus (iz. 11.7 mm), Bacillus cereus (iz. 10 mm) and Escherichia coli (iz. 10.2 mm).\textsuperscript{59, 143, 144} But, it was inactive against Staphylococcus aureus, staphylococcus pyogens, E. coli, Salmonella typhi and Shigella disenteriae. When this extract was mixed with the extract of the fleshy part of Momordica charantia Linn, the combination showed a powerful inhibitory action on Bacillus cereus, Salmonella typhi and Staphylococcus aureus. In addition, chloroform extract was found to be active against Pseudomonas aeruginosa (iz. 8 -14 mm).\textsuperscript{155} These activities enumerated could be due to alkaloids (barakol), steroids, saponins, tannins, resins, glycosides and anthraquinones.\textsuperscript{59, 153, 156} So, barakol (50 mg/kg, ip) was found to be associated with antibacterial activity against Gram+ (Staphylococci aureus, Bacillus subtilis) and Gram- (Escherichia coli, Salmonella thyphi, Salmonella dysenteriae and Pseudomonas aeruginosa).\textsuperscript{3}

These results indicate that C. siamea has very higher potential antibacterial. But, the mechanisms of action were not investigated and need further researches.

**Antifungal effects**

Various fungi species found to be sensitive to hexane, ethanol, methanol and aqueous extract of C. siamea. The ethanol and aqueous bark extract (100 mg/mL) was active on six strains of Candida (C. albicans, C. glabrata, C. tropicalis, C. krusei, C. parapsilosis and C. guilliermondii) and this activity was similar to fluconazole (25 μl/mL) for 24 hours exposition.\textsuperscript{157} But, ethanol leave extract was inactive on C. albicans and Aspergillus fumigatus.\textsuperscript{92} The methanol extracts of this plant (400 μg/mL/27°C for 7days) inhibited Microsporum canis (97.95%), Trichophyton longiﬁsues (92.45%), Fusarium solani (84.53%), Macrophomina phaseolina (76.94%), Trichophyton simii (22.98%), Pseudallescheria boydii (9.91%) and Trichophyton schoenleinii (9.90%). This activity was associated to phenols. But, this extract was inactive on Candida albicans, Trichophyton mentagrophyte, Rhizoctonia solani, Candida lipoiytica, Hanseniaspora uvarum, Pichia membranaeﬁcans, Rhodotorula glutinis, Schizosaccharomyces pombe and Zygosaccharomyces rouxii.\textsuperscript{152}

Hexane extracts of leaves of C. siamea (400 μg/mL/27°C for 7days) inhibited Pseudallescheria boydii, Aspergillus Niger, Microsporum canis, Fusarium solani, and Trichophyton schoenleinii. Its inhibition capacity was similar to those of miconazole and ketoconazole and could be due to sterols and alkaloids-like barakol. This extract was inactive on Trichophyton longiﬂius, Candida albicans, Trichophyton mentagrophytes, Trichophyton simii, Macrophomina phaseolina, and Rhizoctonia solani.\textsuperscript{31, 115, 152, 158} Through studies, we noted that C. siamea could be useful in candidose and against growth of fungi in agricultural products.

**Toxicology**

C. siamea seems less toxic justifying its wide use in folklore medicine.\textsuperscript{70} Indeed, its stem bark’s aqueous extract
(1600 mg/kg; po / 7 weeks) showed less sub-chronic toxicity in male wistar rats.\(^{159}\) This extract and root’s aqueous extracts were found to be relatively not toxic on blood, hepatic and renal cells in wistar rats at 400 mg/kg and 1500 mg/kg; p.o. for 4 weeks, respectively.\(^{23,124}\)

However, at a higher dose, diverse extracts of \textit{C. siamea} showed acute toxicity in various experimental animals’ models. Indeed, its leaves’ ethanol extracts caused mortality of experimental rats with an intraperitoneal \(LD_{50}\) of 9600 mg/kg within 24 h.\(^{160}\) The root’s aqueous extracts (8000 mg/kg, po, 24 hours) showed hypersensitivity reactions, cytotoxicity and increases aggressivity in rats.\(^{40}\) Also, the chronic toxicity studies showed that aqueous extracts (2000 mg/kg; po / 2 weeks, respectively) led to hepatic and renal cell destruction in albinos’ rats.\(^{161}\) This toxicity involved a drastic reduction (p<0.05) in activities of alkaline phosphatase (ALP), aspartate transaminase (AST) and alanine transaminase (ALT) in the liver with a corresponding increase in the serum levels.\(^{162}\) Authors reported that male rat appeared to be more susceptible to the toxic effect of \textit{C. siamea} than female rats.\(^{161}\) In \textit{vivo}, ethanol and aqueous extracts of the leaves were absolutely devoid of toxicity against vero (African green monkey kidney) cells line with IC\(_{50}\) up to 100 μg/ml.\(^{124}\)

In addition, clinical trials using \textit{C. siamea} extracts were investigated. These studies indicate that the crude extract of the leaves in continual oral administration for six months decreased the number of humans’ hematocrit and neutrophiles. The powder induced irritation of the nose, throat and eyes and it increased the rate of transaminase after oral administration.\(^{163}\)

According to the literature, these toxic effects could be due to saponins, glycosides, alkaloids like barakol, anthraquinones and tannins.\(^{160}\) In this review, barakol seems most responsible for \textit{C} \textit{siamea} toxicity. Indeed, in vivo, barakol showed an acute and subacute hepatotoxic effect with \(LD_{50}\) 2330 mg/kg in wistars rats\(^{164}\) and subchronic toxicity effects on blood cells in rats fed with normal and high cholesterol diets\(^{111}\). Barakol produced acute toxicity and death in mice with \(LD_{50}\) 324.09 mg/kg by intraperitoneal injection. Also, barakol may disrupt liver function and an increase of bilirubin in the rats, especially at the dose 240 mg/kg.\(^{148}\)

In vitro, cytotoxicity of barakol (5 mM) on hepatocytes of carp fish (\textit{Cyprinus carpio}) was found after 72 hours of exposure.\(^{165}\) Also, in clinical trials, barakol (40 mg/kg; p.o, 60 days) induced an acute hepatitis in 29-81 years old patients.\(^{166}\) Barakol showed cytotoxic effects in dose and time-dependent manner with IC\(_{50}\) value of 0.68 mM within 96 hours of exposure on humans hepatoma cell line HepG2. Mechanisms involved lactate dehydrogenase leakage, which decreased GSH/GSSG ratio.\(^{167}\) It was also showed that barakol-toxicity was mainly associated to the ROS generation, followed by the ambush of the Bax/Bcl-2 ratio, and caspase-9 activation leading to apoptotic cell death\(^{168}\). Apart from barakol, sennosides of \textit{C. siamea} showed very less hepatotoxicity with \(LD_{50}\) 5000 mg/kg in rat and mice.\(^{132,169}\) Continuous consumption of barakol might not be suitable for health. All toxicity studies showed that the toxic effects of \textit{C. siamea} were reversible after stopping administration.

**Conclusion**

The objective of this article is to show the recent progress in the exploration of \textit{C. siamea} as phyotherapy and to illustrate its potential as a therapeutic agent. With the current information, it is obvious that \textit{C. siamea} has pharmacological functions including antimalaria, antidiabetic, antihypertensive, antioxidant, antitumor, anti-inflammatory, analgesic, antipyretic, anxiolytic, sedative, antibacterial, and antifungal activities. As the current information shows more ninety bioactive compounds were isolated from \textit{C. siamea}. Pharmacological effects of most of these compounds are not yet known. Nevertheless, from the results of studies carried out, it is possible that chromone alkaloids (barakol, cassiarin A), antraquinones (emodin, chrysophanol), and biaantraquinones (cassiamin A, cassiamin B) might be useful in the development of new drugs to treat various diseases. However, the present results suggest a possibility that these compounds can be further developed as a potential disease-curing remedy. It must be kept in mind that clinicians should remain cautious until more definitive studies demonstrate the quality and effectiveness of \textit{C. siamea}. For these reasons, extensive pharmacological and chemical experiments, together with human metabolism will be a focus for future studies. Last but not the least, this review emphasizes the potential of \textit{C. siamea} to be employed in new therapeutic drugs and provide the basis for future researches on the application of transitional medicinal plants.

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