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Cepharanthine: an update of its mode of action, pharmacological properties and medical applications

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Table of content

1. Origin, discovery and development of CEP
2. Anti-oxidative properties - Free radicals scavenging
3. Anti-inflammatory properties - NFκB inhibition
4. Inhibition of drug efflux transporters
5. Binding to proteins: Hsp90 and others
6. Interaction with cell membranes
7. Binding to G-quadruplex nucleic acid structures
8. Vasodilatation effect
9. Anti-proliferative activities - induction of tumor cell death
10. Inhibition of cell migration - anti-metastatic and anti-atherosclerosis properties
11. Inhibition of angiogenesis
12. Anti-cancer activity of CEP in drug combinations
13. Radiosensitization
14. Treatment of radiation-induced leukopenia and thrombocytopenia
15. Immuno-modulation - Treatment of sepsis, chronic immune thrombocytopenia
16. Inhibition of bone resorption
17. Antiviral properties
18. Treatment of alopecia
19. Treatment of snake bites
20. Antiparasitic activities
21. Other activities
22. Discussion and perspective

45 **Abstract**

46

47 **Background.** Cepharanthine (CEP) is a drug used in Japan since the 1950s to treat a number of acute and
48 chronic diseases, including treatment of leukopenia, snake bites, xerostomia and alopecia. It is the only
49 approved drug for Human use in the large class of bisbenzylisoquinoline alkaloids. This natural product,
50 mainly isolated from the plant *Stephania cephalantha* Hayata, exhibits multiple pharmacological properties
51 including anti-oxidative, anti-inflammatory, immuno-regulatory, anti-cancer, anti-viral and anti-parasitic
52 properties.

53

54 **Purpose.** The mechanism of action of CEP is multifactorial. The drug exerts membrane effects (modulation
55 of efflux pumps, membrane rigidification) as well as different intracellular and nuclear effects. CEP
56 interferes with several metabolic axes, primarily with the AMP-activated protein kinase (AMPK) and NFκB
57 signaling pathways. In particular, the anti-inflammatory effects of CEP rely on AMPK activation and NFκB
58 inhibition.

59

60 **Conclusion.** In this review, the historical discovery and development of CEP are retraced, and the key
61 mediators involved in its mode of action are presented. The past, present, and future of CEP are
62 recapitulated. This review also suggests new opportunities to extend the clinical applications of this well-
63 tolerated old Japanese drug.

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68 **Keywords:** Cepharanthine, alkaloids, natural products, inflammation, cancer, *Stephania*.

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71 **Abbreviations:** CEP, cepharanthine; BBIQ, bisbenzylisoquinoline; AMPK, adenosine 5'-monophosphate
72 (AMP)-activated protein kinase; NFκB, nuclear factor κB.

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77 Cepharantine (CEP, Fig. 1) is a natural product and an approved drug used for more than 70 years in Japan
78 to treat a variety of acute and chronic diseases, such as venomous snakebites, alopecia, malaria and a few
79 other pathologies, without major side effects. A variety of biological effects responsible for the clinical
80 activities have been attributed to CEP. In this review, I shall try to summarize the recent findings
81 accumulated with this compound and discuss its therapeutic potential. The history of the drug discovery
82 and development is also highlighted here. The clinical efficacy of CEP has been discussed in previous
83 reviews (Furusawa et al., 2007; Rogosnitsky and Danks, 2011) but an update of its properties and
84 applications is useful.

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88 1. Origin, discovery and development of CEP

89

90 CEP is isolated from plants of the genus *Stephania* which is one of the biggest genera belonging to
91 moonseed family Menispermaceae. The name *Stephania* may come from the Greek stefanos, a crown or
92 garland. This alkaloid is found in several *Stephania* species, principally *S. rotunda* Lour and *S. cephalantha*
93 Hayata (known as « Tamasaki-tsuzurafuji » in Japanese; « jin qian diao wu gui » [金线吊乌龟] in Chinese
94 (Hong et al., 2015); « Binh vô hoa đầu » in Vietnamese), but also in *S. sasakii* Hayata (known as « Koto-
95 tsuzurafuji » in Japanese), *S. suberosa* Forman, *S. epigaea* (Lv et al., 2013) and *S. japonica* (Fig. 2). *Stephania*
96 *rotunda* is a creeper commonly found in the mountainous areas of Cambodia and throughout Southeast
97 Asia (Cambodia, Vietnam, Laos, and India). The plant *Stephania cephalantha* is native to China and Taiwan,
98 where it was used as an indigenous medicine or Chinese herbal medicine. A botanist of Taipei Imperial
99 University, Bunzo Hayata, reported the use of the plant for the first time in 1914. The correct botanical
100 name is *S. cephalantha* although the literature principally mentions the plant as *S. cepharantha*. The vast
101 majority of publications refer to *S. cepharantha* and rarely *S. cephalantha*. It is a very common misspelling.
102 *Stephania* are wild plants, rich in alkaloids, commonly used in traditional food and medicine in Asia for the
103 treatment of fevers.

104

105 More than 600 alkaloids have been isolated from the genus *Stephania* and about 40 different alkaloids
106 were characterized from *S. cephalantha* extracts (Semwal et al., 2010). The chemical composition of
107 extracts varies from one region to another and according to the harvest period. CEP is generally more
108 abundant in the tubers of the plant than the roots and is also found in the leaves and seeds of the plant,
109 which is cultivated in Japan (Desgrouas et al., 2014a). It is important to mention that in certain countries, in
110 France in particular, the use of extracts of *S. cepharantha* is forbidden due to the risk of potential
111 substitution with other toxic plants having similar Chinese names (notably *Aristolochia fanghi*, containing
112 aristolochic acids which are nephrotoxic compounds) (Semwal et al., 2010). The principle of
113 pharmacovigilance applied to herbal medicinal products (or phytovigilance) is now well taken in account by
114 the international health agencies (Lehmann and Pabst, 2016). CEP **has also been detected** in *Radix*
115 *Tinosporae*, a herb used in traditional Chinese medicine for the treatment of various inflammatory
116 diseases (Xiang et al., 2016; Liu et al., 2017). This is perhaps not entirely surprising because *Tinosporae*
117 *Radix* is the dried root tuber of *Tinospora sagittata* (Oliv.) Gagnep., which also belongs to the family
118 Menispermaceae.

119

120 The pharmacist Heisaburo Kondo purified the active ingredient in 1934 from *S. cepharantha* and named it
121 cepharanthine after its binomial nomenclature (Fig. 3). In 1938, a US patent application by Kondo and
122 collaborators **referred** to the preparation of alkaloids from *S. cepharantha* and the isolation of CEP itself.
123 From a chemical point of view, CEP is biscochlorine alkaloid, also known as 12-O-methyl cepharanoline and
124 it belongs to a large family of structurally close bisbenzylisoquinoline (BBIQ) cyclic alkaloids which includes

125 fangchinoline, tetandrine, hernandezine, berbamine, daphnoline, cycleanine (Fig. 4), and many other BBIQ
126 cyclic and non-cyclic, cited in Table 1 (note the unlimited originality of their names). These compounds bear
127 two coclaurine units joined head-to-tail or head-to-head, but the chemical diversity is huge and about 500
128 BBIQs are known in this class (Baghdikian et al., 2013; Weber and Opatz, 2019). In CEP, the two BIQ units
129 are joined head-to-head and the alkaloid has an elliptic macrocyclic structure (Fig. 1).

130
131 Optimized methods for the analysis of these alkaloids in *S. cephalantha* extracts have been reported (Yuan
132 et al., 2013; Liu et al., 2016a; Xiao et al., 2019), as well as green extraction technologies (using ethanol–
133 water mixtures) to purify CEP from *S. rotunda* tuber (Desgrouas et al., 2014b). The content of CEP in *S.*
134 *cephalantha* is 2.9% (Tomita et al., 1968). The natural product, extracted from the plant, is used for
135 medicinal applications. The total synthesis of CEP, first reported in 1967 (Tomita et al., 1967, 1968), is not
136 cost-effective. It should be noted that recently, the absolute configuration of CEP has been reassigned from
137 (1R,1'S) to (1R,1'R) using quantum theory (Ren et al., 2019). The pharmaceutically used form of CEP is a
138 dihydrochloride salt. There are several patents specific to CEP, such as (i) a US patent describing the
139 extraction and purification of CEP from rhizomes of *S. sasakii* Hayata published in 1941; (ii) an European
140 patent application covering the preparation of anti-HIV composition containing CEP in 1992; (iii) A Japanese
141 patent about the preparation CEP for the treatment and prevention of intestinal diseases in 1996; (iv) A
142 Chinese patent describing the method of preparation of CEP hydrochloride filed in 2012; (v) a US patent
143 disclosing the pharmaceutical preparation of CEP and tetrandrine salts and (vi) the production of CEP at the
144 scale of 5-10kg under good manufacturing practice conditions mentioned in a recent US patent.

145
146 CEP was discovered in 1934 and then rapidly tested in Human, based on the traditional use of the medicinal
147 plant. A paper published in 1949 mentions that in 1937 CEP, given in tablets or in liquid, contributed to
148 reduce considerably (from 41% to 22%) the average mortality in patients with severe pulmonary
149 tuberculosis at the Yokohama Sanatorium in Japan (Hasegawa, 1949). At that time, the antitubercular
150 activity of CEP was largely promoted, but later the drug was abandoned, superseded by more active
151 products (Al-Humadi et al., 2017). Nevertheless, the initial successful clinical use of CEP for the treatment of
152 tuberculosis has encouraged its use in other pathological indications (e.g. pertussis, leprosy and lupus
153 vulgaris) and associated research activities to elucidate its mode of action. The biochemical and biological
154 properties, and clinical applications of CEP are reviewed below.

155 156 157 **2. Anti-oxidative properties - Free radicals scavenging**

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159 Reactive oxygen radicals (ROS), generated metabolically or induced by radiations or chemicals, can
160 engender cell damages, in particular, lesions of nucleic acids. Accumulated DNA damages can be
161 deleterious and toxic to cells, via DNA strand breaks and/or the accumulation of mutations and other types
162 of molecular rearrangements. CEP can protect nuclear DNA from the damages induced by endogenous
163 oxidants, most likely via its antioxidant properties (Halicka et al., 2008). The scavenging properties of CEP
164 also provide a protection of DNA from the radicals generated endogenously during oxidative metabolism.
165 The drug can also reduce the generation of radicals through activation of NADH oxidase (Matsuno et al.,
166 1990). CEP has effective ferrous ion (Fe²⁺) chelating capacity, similar to EDTA for example. The anti-lipid
167 peroxidation activity of CEP is also due to its direct radical scavenging activity (Kogure et al., 2003). One of
168 the two amine moieties in the CEP molecule is responsible for the radical scavenging activity (Kogure et al.,
169 1999). Many BBIQ alkaloids show antioxidant activities.

170 171 172 **3. Anti-inflammatory properties - NFκB inhibition**

173

174 The anti-inflammatory effects of CEP are in large part at the origin of the extensive use of *S. cephalantha*
175 extracts in folk medicine for the treatment of rheumatism, lumbago, nephritis edema, dysentery and other
176 inflammatory diseases. The capacity of CEP to reduce the production of oxidants leads subsequently to the
177 mitigation of the transcription factor NFκB which is a potent regulator of inflammatory molecules. CEP
178 reduces NFκB expression. The anti-inflammatory potential of CEP can be useful in a variety of pathological
179 situations. For example, the capacity of CEP to inhibit inflammation and oxidation leads to protective effect
180 against muscle and kidney injuries induced by limb ischemia/reperfusion (Chang et al., 2016). CEP was also
181 found to ameliorate diabetic nephropathy in a rat model, through inhibition of NFκB and decreased levels
182 of IL-1β and TNF-α (Samra et al., 2016). The drug mitigates pro-inflammatory cytokine response in lung
183 injury induced by hemorrhagic shock/resuscitation in rats (Kao et al., 2015). The release of the pro-
184 inflammatory cytokines TNF-α, IL-1β and IL-6 was found to be reduced after treatment with CEP in cell and
185 mouse models of LPS-induced inflammation and the protective effects occur, at least in part, via NFκB
186 inhibition. Indeed, in a mouse model of lipopolysaccharide (LPS)-induced mastitis, CEP inhibited the
187 phosphorylation of NFκB p65 subunit and the degradation of its inhibitor IκBα (Ershun et al., 2014), thereby
188 inhibiting the translocation of NFκB from cytosol to nucleus (Paudel et al., 2016). However, recently CEP
189 was found to prevent the phosphorylation of JAK2 and STAT1, but did not interfere with the NFκB pathway
190 (Aota et al., 2018). In this cell model, CEP inhibited the production of the chemokine CXCL10 induced by
191 IFN-γ, via inhibition of the JAK2/STAT1 signaling pathway (Lv et al., 2013). Inhibition of NFκB is a mechanism
192 common to several BBIQs. In particular, tetrandrine was shown to inhibit IκBα and NFκB p65
193 phosphorylation and this effect account, at least in part, for its anti-inflammatory properties (Gao et al.,
194 2016; Xu et al., 2016). Berbamine, another BBIQ, also exerts anti-inflammatory effects via inhibition of NFκB
195 and MAPK signaling (Jia et al., 2017). Neferine also inhibits the activation of the NFκB signaling pathway and
196 prevents its nuclear translocation (Liu et al., 2018).

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199 **4. Inhibition of drug efflux transporters**

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201 The overexpression of drug transporters on the membrane of cancer cells is a major cause of multi-drug
202 resistance to cancer chemotherapy. Among the many transporters, ABCC10 (also known as MRP7) can be
203 inhibited by a variety of drugs including certain kinase inhibitors (lapatinib, erlotinib, imatinib) and different
204 natural products such as CEP. This natural product can reverse **completely** the resistance to paclitaxel of
205 cells expressing ABCC10, increasing the intracellular accumulation of the anticancer agent and inhibiting its
206 efflux (Zhou et al., 2009). The synergy between CEP and paclitaxel has led to the design of co-loaded
207 polymeric nanoparticles that proved active against gastric cancer models in vitro and in vivo (Yu et al.,
208 2016). ABCC10 is a broad-specificity transporter of xenobiotics, including many antitumor drugs (taxanes,
209 epothilone B, vinca alkaloids, cytarabine, tamoxifen). Therefore, CEP can promote the anticancer activity of
210 most of these compounds. But CEP can also interfere with other transporters, in particular ABCB1 (also
211 known as MDR1 or P-gp) and ABCC1 (MRP1). CEP can be used to reverse resistance to many cytotoxic
212 agents and thus to sensitize tumors to certain chemotherapeutic substances (Kathawala et al., 2014). It
213 potently enhances the sensitivity to cytotoxic agents such as doxorubicin in K562 leukemia cells, not only
214 via a reversal of ABCB1-mediated multi-drug resistance (MDR) but also increasing the accumulation of
215 doxorubicin in nuclei (Ikeda et al., 2005). The suppression of ABCB1 function by CEP would derive from an
216 inhibition of the PI3K/Akt signaling pathway. Inhibition of PI3K/Akt pathway by CEP leads to a down-
217 regulation of ABCB1 expression and then MDR-reversion in ovarian cancer cells (Huang et al., 2017). But a
218 direct interaction of CEP with specific drug transporters at the plasma membrane or via an indirect lipid-
219 mediated effect cannot be excluded. For example, the related BBIQ neferine is believed to bind directly to
220 ABCB1 (Kadioglu et al., 2017).

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5. Binding to proteins: Hsp90 and others

The heat shock protein 90 kDa (Hsp90) has attracted significant interest as a viable drug target, particularly for cancer. Inhibitors targeting the ATPase domain of Hsp90 demonstrate potent anti-proliferative effects, but have failed clinical trials due to associated toxicities. Interestingly, it has been reported that CEP interacts with the middle domain of Hsp90 α more strongly than the 3 other biscochlorine alkaloids berbamine, isotetrandrine and cycleanine (Haginaka et al., 2013). The interaction of CEP with Hsp90 and other molecular chaperone proteins, deserves further studies. CEP also inhibited another ATPase, namely Na(+),K(+)-ATPase, although in this case the inhibition by CEP is much less potent than inhibition by cycleanine (Sato et al., 2003).

6. Interaction with cell membranes

Early Japanese studies pointed out that CEP is a membrane-interacting and -stabilizing agent (Shinoda et al., 1990). The drug reduces the plasma membrane fluidity suggesting a direct interaction with the lipid bilayer. The amphipathic character of CEP facilitates its interaction with cell membranes, increasing permeability and interaction with lipophilic compounds. The membrane effects would be at the origin of the inhibition of snake venom-induced hemolysis by CEP (Morikawa et al., 1992) and the drug-induced enhancement of fatty acid synthesis in rat white adipocytes (Ohkura et al., 2001). The drug does not directly act on the insulin-involved glucose metabolism but by changing the cell membrane condition, it modifies the cell response to insulin (Ohkura and Hori, 2001). The membrane effects of CEP might also be implicated in the capacity of the drug to enhance the thermosensitivity of cancer cells, acting as a mild thermosensitizer (Yamamoto et al., 1999). The membrane stabilization effect of CEP is a prime element of its mode of action. Intracellular membranes are also affected. CEP can inhibit the endolysosomal trafficking of free-cholesterol and low-density lipoproteins, leading to the dissociation of mTOR from lysosomes and inhibition of its downstream signaling. This effect may directly contribute to the drug-induced inhibition of angiogenesis and tumor growth (Lyu et al., 2017).

7. Binding to G-quadruplex nucleic acid structures

Two independent studies have reported that CEP can bind and stabilize G-quadruplex formed by G- rich sequences in DNA and RNA. G-quadruplex DNA are DNA secondary structures formed from planar stacks of guanine tetrads stabilized by Hoogsteen hydrogen bonding. Certain small molecules have the capacity to stabilize these structures. CEP was found to stabilize a G-quadruplex DNA existing in the 3'-flanking region of the STAT3 gene, thereby decreasing the expression of STAT3 in cultured cardiomyocytes (Lin et al., 2011). G-quadruplexes also exist in RNA, in particular telomeric RNA to regulate telomerase activity. CEP was found to bind tightly to two types of G-quadruplex telomeric RNA sequences, with an affinity higher than that of its analogs fangchinoline and tetandrine (Cui et al., 2012). This G-quadruplex stabilization property may contribute to the anticancer activity of CEP.

8. Vasodilatation effect

268 The cutaneous microcirculatory effects of CEP have been investigated. The drug induces notable and
269 transient vasodilatation with vasomotion. Vasodilation and improvement of peripheral circulation was also
270 noted in early study suggesting a beneficial use to treat sickle-cell patients (Ohnishi, 1983). The
271 vasodilator effects of CEP improved cutaneous microcirculation in a rabbit model (Asano et al., 1987).
272 This effect on the microcirculation, coupled with the potent anti-inflammatory activity, speak for the use of
273 CEP to treat certain dermatological and orofacial inflammatory lesions, such as oral lichen planus (Moritani
274 et al., 2018). In early studies, the vasodilator effects of CEP was also evidenced using isolated vessels from
275 rats and CEP proved more efficient than its analogs isotetrandrine and berbamine (Kamiya et al., 1993).
276 Similarly, the related BBIQ alkaloid curine has been described as a vasodilator (Medeiros et al., 2011).

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279 **9. Anti-proliferative activities - induction of tumor cell death**

280

281 CEP inhibits the proliferation of different cell types in vitro, including many cancer cell lines, T-cell lines and
282 peripheral mononuclear cells (PBMC). The IC50s are usually in the 1-10 μ M range and the drug is non-
283 mutagenic. CEP can trigger apoptosis, via the activation of caspases and DNA fragmentation. The drug
284 affects the cell cycle, generally arresting cells in the G1 and S phases. A mechanistic study using
285 hepatocellular carcinoma HuH-7 cells revealed that CEP induces chromatin condensation and nuclear
286 fragmentation, likely resulting from an oxidative stress and activation of stress activated kinase JNK1/2,
287 MAPK p38 and ERK (Biswas et al., 2006). Induction of apoptosis by CEP has been observed in many cell
288 types : dendritic cells (Uto et al., 2016), primary effusion lymphoma (Takahashi-Makise et al., 2009),
289 leukemia cells (Wu et al., 2002), melanoma cells (Zhu et al., 2017), cholangiocarcinoma (Seubwai et al.,
290 2010), ovarian cancer cells (Payon et al., 2019), myeloma cells (Kikukawa et al., 2008), osteosarcoma cells
291 (Chen et al., 2012) and breast cancer cells (Gao et al., 2017). In colorectal cancer cells, cell cycle arrest and
292 apoptosis may be mediated through up-regulation of p21Waf1/Cip1, down-regulation of cyclin A and Bcl-2
293 and induction of ROS production (Rattanawong et al., 2018). In fact, the mechanism of apoptosis caused by
294 CEP is complex, likely cell-type dependent, and plurimodal. A direct interaction with mitochondria in cells
295 has been reported, inhibiting Ca^{2+} -induced swelling, depolarization, cytochrome c and Ca^{2+} releases
296 (Nagano et al., 2003). CEP-induced mitochondrial dysfunctions were noted in several cancer cell types (Hua
297 et al., 2015).

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299 Both drug-induced apoptosis and autophagy were noted in breast cancer cells, possibly linked to
300 perturbation of the AKT /mTOR signaling pathway (Gao et al., 2017). Law and coworkers reported that CEP
301 induces autophagic cell death via an activation of the AMPK kinase activity (Law et al. 2014). The
302 biscochlorine hernandezine, which is structurally close to CEP, can trigger cell death via an activation of the
303 AMPK-mTOR signaling cascade and its cytotoxic action is independent of apoptosis (Law et al., 2016).
304 Similar data were reported with CEP, and this capacity to enhance autophagy likely contributes to its
305 anticancer activity (Law et al., 2014). This is significant considering that most chemotherapy-resistant
306 cancers have defective apoptotic pathways. The direct activation of AMPK by CEP may be beneficial not
307 only to trigger cancer cell death but also in other pathologies, in particular metabolic disorders, considering
308 the implication of AMPK in glucose and lipid metabolisms. AMPK activation is a key property of CEP and
309 related biscochlorine alkaloids.

310 There are numerous anticancer in vitro studies with CEP but fewer studies in vivo. Interestingly, a modest
311 but significant antitumor activity has been reported in a xenograft model of SaOS2 osteosarcoma cells.
312 Treatment of tumor-bearing mice with CEP at 20 mg/kg/day for 20 days led to a reduction of tumor volume
313 and a diminished expression of STAT3 in the residual tumor (Chen et al., 2012). A significant inhibition of
314 tumor growth and infiltration was also observed after CEP treatment of immunodeficient mice inoculated
315 with a primary effusion lymphoma. The antitumor activity would result from the capacity of CEP to

316 abrogate the NFκB activity by blocking phosphorylation of p65 subunit, inhibiting thus nuclear translocation
317 of NFκB and its binding to DNA (Takahashi-Makise et al., 2009; Seubwai et al., 2010). In a xenograft model
318 of choroidal melanoma, CEP (25mg/kg, 5 times/week for 4 weeks) reduced tumor growth and the effect
319 was associated with an activation (phosphorylation) of JNK1/2 (Zhu et al., 2017).

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321

322 **10. Inhibition of cell migration - anti-metastatic and anti-atherosclerosis properties**

323

324 Migration and proliferation are common characteristics of cancer cells and vascular smooth muscle cells
325 (VSMC). In both situations, CEP has been shown to inhibit the motility of the cells and their growth. The
326 anti-migratory effect of CEP on VSMCs is due to its inhibitory effect on **matrix** metalloproteinase (MMP)-9
327 expression, preventing the degradation of extracellular matrix components. This effect, coupled with
328 attenuation of inflammation and lipid peroxidation, confers to CEP anti-atherosclerosis properties (Paudel
329 et al., 2016). A CEP-induced suppression of MMP-9 production was also observed in human salivary gland
330 acinar cells, via a down-regulation of NFκB (Azuma et al., 2002). The inhibition of MMP-9 by CEP prevents
331 the destruction of the acinar structure in the salivary glands of patients with Sjögren's syndrome (Azuma et
332 al., 2006). Similar properties are invoked to account for the anti-metastatic effects of CEP. The drug
333 suppresses the metastatic potential of cholangiocarcinoma cells by reducing cell motility and invasion, via a
334 mechanism potentially involving suppression of adhesion molecules (ICAM-1) and matrix metalloproteinase
335 (MMP)-2 (Uthaisar et al., 2012). Other biscochlorine alkaloids structurally close to CEP, such as
336 fangchinoline (Chen et al., 2017) and tetrandrine (Zhang et al., 2018) were found to exhibit anti-metastatic
337 effects as well. Interestingly, the anti-metastatic activity of fangchinoline in human gastric cancer cells was
338 also found to implicate the suppression of MMP-2 and MMP-9, increase of TIMP1 and TIMP2 genes, and
339 inhibition of AKT phosphorylation (Chen et al., 2017). Fangchinoline inhibits metastasis and migration of
340 melanoma and glioma cells in vitro, as well as it suppresses in a dose-dependent manner the adhesion,
341 migration, and invasion human gastric cancer cells (Mérarchi et al., 2018). Tetrandrine inhibits
342 hepatocellular carcinoma cell invasion and migration by repressing the autophagy-dependent Wnt/β-
343 catenin and metastatic tumor antigen 1 (MTA1) signaling pathways (Zhang et al., 2018).

344

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346 **11. Inhibition of angiogenesis**

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348 The formation of tubule networks of human umbilical vein endothelial cells (HUVEC) and human dermal
349 microvascular endothelial cells (HMVEC) is a classical in vitro model to evaluate the anti-angiogenic effects
350 of drugs. CEP inhibits VEGF-promoted tubule formation in HUVECs, an effect that is likely associated with
351 the inhibition of VEGF and IL-8 expression involved in the **block**ade of NFκB activity (Harada et al., 2009).
352 CEP was also found to inhibit angiogenesis in HUVEC and in zebrafish in a cholesterol-dependent manner,
353 as mentioned above (Lyu et al., 2017).

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356 **12. Anti-cancer activity of CEP in drug combinations**

357

358 Owing to its capacity to modulate drug transporters such as PgP and MRP7, CEP can be combined with
359 various drugs. Synergistic effects have been observed with different anticancer drugs, such as the
360 tetramethylnaphthalene anti-viral derivative TMNAA (Toyama et al., 2012), the nitrosourea nimustine
361 (Kono et al., 2002), the anthracycline doxorubicin (Nakajima et al., 2004), the taxanes paclitaxel and
362 docetaxel (Malofeeva et al., 2012), the recently approved new pan-EGFR inhibitor dacomitinib (Tang et al.,
363 2018), and other anticancer agents (Ita et al., 2008). CEP enhances the antitumor activity of cisplatin in lung

364 and breast cancer xenografts in mice (Mukai et al., 2003). Its capacity to downregulate the mRNA
365 expression of MDR1 and P-gp, through activation of c-Jun and enhancement of p21 expression, leads to an
366 increase sensitivity of the tumor to cisplatin treatment (Zhou et al., 2017). Interestingly, CEP not only
367 promotes the anticancer activity of cisplatin, via an inhibition of P-gp but it can also reduce its renal toxicity
368 through an induced expression of metallothionein (Sogawa et al., 2013). In K562/MDR leukemia cells, CEP
369 was found to be very effective for the reversal of the resistance to imatinib (Mukai et al., 2003). Recently, it
370 was shown that the combination of CEP and 5-fluorouracil additively induced apoptotic and necrotic cell
371 death, via an upregulation of the expression of BAK and cleaved PARP in HT-29 human colorectal cancer
372 cells harboring mutant p53, both in vitro and in vivo (Unson et al., 2019). Tumor necrosis factor-related
373 apoptosis-inducing ligand (TRAIL) functions as a selective apoptosis-inducing ligand in cancer cells with
374 normal cells remaining unaffected. CEP enhances TRAIL-mediated apoptosis through a down-regulation of
375 survivin expression, not by direct inhibition of survivin mRNA expression but via a downregulation of a
376 deubiquitin protein that modulates survivin expression in renal carcinoma cells (Shahriyar et al., 2018).

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379 **13. Radiosensitization**

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381 Radiotherapy is often used for the treatment of oral squamous carcinoma, the most common epithelial
382 malignancy in the oral cavity, frequently observed in patients who smoke and drink heavily. CEP was found
383 to improve the response to radiotherapy in oral squamous carcinoma cell lines. The drug exhibited a strong
384 inhibitory effect on DNA double-strand break repair after radiation and the combined therapy markedly
385 increased tumor cell apoptosis. The combination of CEP plus radiation caused growth inhibition and tumor
386 regression of tumors in mice (Harada et al., 2012). CEP inhibits the production of irradiation-induced IL-6
387 and IL-8, which are downstream targets of NFκB (Tamatani et al., 2013). A similar radiation sensitization by
388 CEP was also reported using the human cervical adenocarcinoma HeLa cell line. In this case, CEP efficiently
389 decreased ionizing radiation-induced STAT3 and COX-2 activation. In vivo administration of CEP combined
390 with radiation in HeLa xenografts enhanced tumor growth delay and apoptosis, with reduced expression of
391 STAT3, Bcl-2, c-Myc, and COX-2 (Fang et al., 2013).

392
393

394 **14. Treatment of radiation-induced leukopenia and thrombocytopenia**

395

396 Administration of CEP to accelerate the recovery from leukopenia after X-ray irradiation (or mitomycin
397 treatment) in cancer therapy is one of the classical and well-established use of the alkaloid. The beneficial
398 effect of CEP on leukopenia was first noted in 1965 and then firmly demonstrated in the early 1980s
399 (Oyaizu et al., 2001). The drug can be used to treat but also to prevent from leukopenia, especially
400 neutropenia, in patients treated with anticancer drugs. A large multi-center clinical study demonstrated
401 that CEP is safe and significantly effective for the management of leukopenia caused by radiotherapy,
402 protecting leukocytes from the damaging effects of radiations and showing no effect on erythrocyte and
403 platelet counts, according to this retrospective study (Kanamori et al., 2016). However, other studies
404 indicated that CEP has the capacity not only to limit the platelet destruction process but also to facilitate
405 the platelet production process, via a drug-induced increase of the number of colony-forming unit of
406 megakaryocytes (Sato et al., 2001). Thus, CEP may prolong the platelet lifespan.

407
408

409 **15. Immuno-modulation - Treatment of sepsis, chronic immune thrombocytopenia**

410

411 CEP therapy, alone or in combination with prednisolone, improves symptoms of chronic immune
412 thrombocytopenia (Takahata et al., 2012). The drug was found to be effective in halting the progression of
413 immune thrombocytopenic purpura in a patient with multiple myeloma (Tabata et al., 2012). A link can be
414 established between the capacity of CEP to inhibit the platelet activation and its capacity to alter
415 phospholipid dynamics and functions. This is coherent with early studies showing that inhibition of platelet
416 aggregation by CEP is accomplished during the early, membrane-related activation process. A recent study
417 conducted in a pediatric population also underlined the useful effect of CEP for the management of chronic
418 immune thrombocytopenia (Yamazaki et al., 2017).

419
420 CEP can reduce the production of IL-6 and TNF- α in LPS-stimulated dendritic cells (Uto et al., 2011). The
421 potent anti-inflammatory activity of CEP speaks for the potential use of the drug for treating systemic
422 inflammatory response syndromes such as sepsis. Along these lines, CEP was found to attenuate acute lung
423 injury and septic shock after smoke inhalation in sheep (Murakami et al., 2003). Treatment with CEP was
424 also found to delay lethal shock induced by an infection with a mutant of *Salmonella typhimurium*
425 (Maruyama et al., 2000). A later study revealed that CEP could have a preventive effect on the lethal action
426 of endotoxin or TNF α -induced lethal shock, through a suppression of nitric oxide production in
427 macrophages (Sakaguchi et al., 2007). As a potent immunoregulatory agent, CEP may have a strong
428 potential against various autoimmune diseases and allergy.

429

430

431 **16. Inhibition of bone resorption**

432

433 CEP has been shown to inhibit osteoclast formation in a model of estrogen deficiency-induced osteoporosis
434 in vivo, without affecting bone formation. Apparently, the attenuation of osteoclastogenesis results from
435 the impairment of the JNK and PI3K-AKT signaling pathways (Zhou et al., 2018). CEP inhibits the
436 phosphorylation of JNK (a member of the MAPK family) and suppresses RANKL-induced phosphorylation of
437 PI3K and AKT, thereby impairing osteoclastogenesis. In another recent study, CEP was also found to inhibit
438 the expression of several osteoclast-differentiation marker genes and to inhibit RANKL-induced osteoclast
439 formation (Lin et al., 2018). These two recent works suggest that CEP might be useful to prevent
440 osteoporosis. Tetrandrine was also shown to attenuate bone erosion in a model of collagen-induced
441 arthritis (Jia et al., 2018).

442

443

444 **17. Antiviral properties**

445

446 The capacity of CEP to suppress the production of inflammatory cytokines and chemokines in cells is at the
447 origin of its antiviral activity. The anti-HIV activity of CEP was first mentioned in a patent application from
448 1991. The drug can inhibit HIV-1 replication in latently infected U1 cells, through inhibition of NF κ B which is
449 a potent inducer of HIV-1 gene expression. It is a highly potent inhibitor of HIV-1 replication in chronically
450 infected monocytic cells (Okamoto et al., 1998). This property, coupled with its capacity to cross the blood-
451 brain barrier and induce neural cell death, make CEP a potential agent against HIV-1 encephalopathy
452 (Okamoto et al., 2001). The anti-HIV-1 activity not only relies on NF κ B inhibition but also CEP-induced
453 inhibition of the HIV-1 entry process by reducing plasma membrane fluidity (Matsuda et al., 2014).
454 Synthetic derivatives of CEP endowed with more potent anti-HIV-1 activities have been described.
455 Replacement of the 12-O-methyl group of CEP with a 12-O-ethylpiperazinyl substituent reinforces the
456 activity against HIV-1 replication (Baba et al., 2001). The drug can also affect the replication of other
457 viruses, in particular it was found to be active against both wild-type and lamivudine-resistant clinical
458 isolates of the hepatitis B virus (Zhou et al., 2012) and early studies demonstrated an activity against

459 Herpes zoster. CEP exhibits strong anti-HSV1 activity (Liu et al., 2004) and proved active against human T-
460 lymphotropic virus type 1 (HTLV-1)-infected T-cell lines when combined with the tetramethylnaphthalene
461 derivative TMNAA (Toyama et al., 2012). Finally, an activity against severe acute respiratory syndrome
462 (SARS)-related coronaviruses has been also reported (Zhang et al., 2005).

463
464 Interestingly, molecular docking simulations predicted that CEP could bind to protein targets of the Ebola
465 virus (Uzochukwu et al., 2016). **The US company Texas Biomed is** developing a more bioavailable, or more
466 easily absorbed, formulation of CEP, which might be combined with chloroquine to combat the Ebola virus.

467
468

469 **18. Treatment of alopecia**

470

471 CEP is used for the treatment of alopecia areata, also known as spot baldness, an autoimmune disorder
472 which can be treated with topical corticosteroids and/or minoxidil (Hon and Leung, 2011). The first
473 publications describing the therapy of alopecia with CEP date from 1956 in French and 1969 in Japanese
474 (Fig. 3). The anti-alopecia activity of CEP was promoted already in the mid-1950s and remains largely cited
475 today. But over the past 50 years, very limited scientific evidences have been published to confirm and
476 demonstrate the efficacy of CEP to treat alopecia. CEP can protect against aminoglycoside-induced hair cell
477 death (Ou et al., 2009) and it can stimulate cell proliferation and delayed initiation of differentiation and
478 keratinization of the cultured murine cells the hair apparatus (Tanigaki-Obana, 1992). It can also promote
479 the proliferation of cultured hair cells from the murine skin (Nakaoji et al., 1997). The capacity of CEP to
480 stimulate hair growth may result from the drug-induced production of IGF-1 which is an anagen-prolonging
481 growth factor, in dermal papilla cells (Inui and Itami, 2013). A more recent study describing the use of
482 topical lipoid CEP (a lotion at 0.1% CEP) showed only a minor (and not statistically significant) effect on the
483 density, growth rate and thickness of hairs (Inui et al., 2016). Clearly, the use of CEP for the treatment of
484 alopecia areata is not supported by sufficient pharmacological and clinical evidence. However, the drug or
485 an extract of *S. cephalantha* can be found in different non-medical topical lotions commercialized in Japan.

486

487

488 **19. Treatment of snake bites**

489

490 This is another historical use of CEP: the treatment of mamushi bites, a specific pit viper (*Gloydius*
491 *blomhoffii*) found throughout Japan. It is also seen in China and Korea. Mamushi bites cause severe swelling
492 (causing compression of peripheral arteries and/or compartment syndrome of the extremities) and pain
493 that spreads gradually from the bite site. In general, the platelet count gradually decreases due to the
494 platelet aggregation activity of the venom. Both antiserum and CEP are widely used for the treatment of
495 mamushi snakebites. After the bite, the rapid use of an antivenom is essential to neutralize both the
496 hemorrhagic and lethal activities of the venom. CEP has been proposed as a possible alternative therapy to
497 antivenom, to lessen the inflammation and the pain caused by the snake bite (Hifumi et al., 2011). In the
498 severe cases of bites, the antivenom is the major treatment recommended. The use of CEP alone is not
499 recommended as it cannot neutralize the circulating venom (Hifumi et al., 2013). In 2000, Abe and
500 coworkers showed that CEP inhibits two species of phospholipase B (α and β) purified from the venom of
501 the giant hornet (*Vespa mandarinia*) (Abe et al., 2000).

502

503

504 **20. Antiparasitic activities**

505

506 CEP has been shown to be a trypanothione reductase inhibitor (Fournet et al., 1998), an enzyme considered
507 as a robust target to find drugs against Leishmaniasis and the Chagas disease. But the antiparasitic activity
508 of CEP is very limited (Fournet et al., 2000). However, CEP potently enhances the sensitivity of the malaria
509 pathogen *Plasmodium falciparum* to chloroquine (Haruki et al., 2000). CEP has a modest direct inhibitory
510 effect on the trophozoite stage of parasite growth, but acts as a modulator of resistance, capable of
511 prolonging the clinical utility of chloroquine (Tamez et al., 2005). The cepharanthine-chloroquine
512 association is synergistic (Chea et al., 2007). The combination of CEP with chloroquine (or amodiaquine)
513 improved significantly the survival of mice and extended the delay for parasitic recrudescence (Desgrouas
514 et al., 2014c). CEP blocks *P. falciparum* development in ring stage, affecting multiple metabolic pathways,
515 such as cell-cell interactions, glycolysis and isoprenoid pathways (Desgrouas et al., 2014d). These data are
516 consistent with the use of *Stephania* extracts in traditional medicine for the treatment of malaria-related
517 fever.

518

519

520 **21. Other activities**

521

522 Other types of bioactivity have been attributed to CEP, linked to its anti-inflammatory and anti-oxidant
523 properties. Notably, a potent anti-atherosclerotic effect through attenuation of inflammation, lipid
524 peroxidation and vascular smooth muscle cell migration and proliferation, has been described (Paudel et
525 al., 2016). Similarly, CEP might be useful to halt the progression of diabetic nephropathy, caused by an
526 elevation of oxidative stress and proinflammatory cytokines in situations of hyperglycemia (Samra et al.,
527 2016). CEP was also found to selectively inhibit the binding of amyloid- β oligomers to Ephrin type-B
528 receptor 2 (EphB2) and A- β oligomers are believed to be key molecules involved in the pathogenesis of
529 Alzheimer's disease (Suzuki et al., 2016). NF κ B is also considered a promising target for inflammation-based
530 Alzheimer's disease therapy and many phytochemicals able to interfere with the NF κ B pathway are
531 considered for the treatment of this most prevalent form of dementia (Seo et al., 2018).

532

533 CEP might also be useful to treat human autoimmune thyroid diseases, via its capacity to block T-cell
534 activation by thyroglobulin peptides (Li et al., 2016). In this later case, CEP was first identified using a virtual
535 in silico screening procedure from a library of approved drugs and its capacity to inhibit peptide binding to
536 a HLA-DR variant protein and to block T-cells activation in vitro and in vivo were confirmed experimentally
537 (Li et al., 2016). This discovery opens a new clinical field to explore the use of CEP for the treatment of
538 different autoimmune disorders such as arthritis or Sjögren's syndrome. And last, more exotically, CEP was
539 tested as an antifouling compound for marine paints but was found to be less active than other alkaloids
540 such as camptothecin (Feng et al., 2018).

541

542 CEP has probably other unanticipated targets and properties. In particular, an action on certain ion
543 channels may be envisioned considering the activity of related products. Recently, tetrandrine was found to
544 be a potent and selective inhibitor of the Ether-à-go-go-1 (Eag1) ion channel that plays important roles in
545 tumor proliferation, malignant transformation, invasion and metastasis (Wang et al., 2019). However, the
546 structural analogy between the two BBIQ is not sufficient to suspect an activity. For example, the BBIQs
547 berbamine and fangchinoline were found to bind to the water transporting protein aquaporin-4 expressed
548 in the CNS whereas CEP and cycleanine were found to be inactive (Tradtrantip et al., 2012).

549

550

551 **22. Discussion and perspective**

552

553 CEP is a well-established alkaloid, known for 85 years and the only cyclic BBIQ used in the clinic to treat
554 Human diseases. But surprisingly it has not been extensively studied. For example, a search through of the
555 PubMed database gave 331 references for CEP versus 910 for the related BBIQ tetrandrine which is not
556 used clinically (Table 1). As presented here, CEP was discovered in 1934, launched in Japan in 1951 and
557 remains used in the clinic today for the treatment of a variety of diseases and symptoms (Fig. 3). It was
558 initially considered as a promising drug for the treatment of tuberculosis, but today the alkaloid is
559 principally used for its anti-inflammatory, immuno-modulatory properties, notably for the treatment of
560 anemia, alopecia and snake bites. The drug can be administered in large dose and over a long term, either
561 orally or intravenously. It is important to underline that this plant natural product is safe, well tolerated,
562 inducing very limited undesirable effects. Side effects are said to be insignificant and rarely appearing.
563

564 Today CEP remains almost exclusively prescribed in Japan (99% Japan, 1% South Korea), principally in the
565 form of 1mg tablets orally administered, although the bioavailability of CEP by the oral route is limited
566 (Deng et al., 2017). Each tablet (100mg) contains 1% CEP mixed with lactose, talc, calcium stearate,
567 magnesium stearate etc. (mainly from KAKEN SHOYAKU, Japan). The usual oral dosage for the treatment of
568 alopecia areata in adults is 1.5-2 mg CEP per day divided in 2-3 doses taken after meals. The dosage is
569 generally higher (3-6 mg/day) for the treatment of leukopenia and usually 1 mg/day for the treatment of
570 bronchial asthma. There is also a liquid form, corresponding to 1ml or 2ml vials with 0.5% CEP in a fluid
571 solution (2% benzyl alcohol, 1% NaCl and HCl acid) for injection, but this form is more rarely used. Over the
572 past five years, the pharmaceutical sales of CEP-containing products remained relatively stable, with a
573 slight increase of the volume of products (+8% from 2014 to 2018) but a decrease of the associated
574 economic impact (-14% over the same 5-years period), as illustrated in Fig. 5. CEP is an inexpensive drug.
575 The sale volumes are limited, corresponding to a very niche and national market. But the drug is well
576 introduced in Japan, being authorized for 68 years now.
577

578 In 2011 Rogosnitzky and Danks concluded that CEP is a fascinating agent with a complex set of physiological
579 actions and an array of clinical benefits (Rogosnitzky and Danks, 2011). Eight years later, the same
580 conclusion can be reinforced. New properties have been discovered, such as the capacity of CEP to bind to
581 quadruplex nucleic acids and to inhibit of bone resorption. It is difficult to summarize its multimodal
582 mechanism of actions but a tentative scheme can be delineated (Fig. 6). The mode of action is complex,
583 implicating effects at the plasma membrane (inhibition of drug efflux pumps, membrane rigidification),
584 nuclear effects (G4 stabilization; modulation of gene expression) and cytoplasmic activities, in particular a
585 regulation of the AMPK and NF κ B signaling pathways. With no doubt, the AMPK-NF κ B axis is central to the
586 mode of action of CEP. Accumulating evidence from studies with various drug types indicate that AMPK
587 activation promotes anti-inflammatory responses in cells exposed to stress/danger signals mainly through
588 inhibition of NF κ B signaling. There are many examples showing that activation of AMPK is linked to
589 inhibition of NF κ B and suppression of the downstream biological effects, such as autophagy activation (Zhai
590 et al., 2018). Moreover, AMPK exerts also a protective role on the antioxidant defense system. Therefore,
591 AMPK activation by CEP can also contribute to the antioxidant effects. Several studies promote the
592 development of AMPK-targeted therapeutics to treat inflammation and related diseases. In this context,
593 the use of CEP as an AMPK activator/NF κ B inhibitor should be encouraged. It is worth noting also that the
594 AMPK-NF κ B axis has been invoked to explain the bioactivity of other BBIQs, in particular the anti-
595 inflammatory activity of neferine (Guolan et al., 2018) and the induction of apoptosis by isolensinine (Zhang
596 et al., 2015). AMPK, the so-called "cellular energy regulator", might well be the pivotal regulator of CEP
597 bioactivity. But in some cases, the Ras/Erk signaling axis seems to be predominantly implicated, notably to
598 regulate cells growth. Interestingly, the related BBIQ krukovine also represses the growth and proliferation
599 of cancer cells by inactivating AKT signaling pathway and downregulating the RAF-ERK signaling pathway
600 (Lai et al., 2018).

601

602 More generally, CEP can be qualified as a protector and a promotor. The drug protects cells, from lipid
603 oxidation, from oxidative DNA damages, from pro-inflammatory cytokines production. At the same time, it
604 promotes the activity of combined drugs and radiations for the treatment of cancer and malaria for
605 examples. One third of the publications on CEP refers to cancer, through the study of drug- induced cell
606 death (apoptosis, autophagy) and drug combinations. But these are mechanistic studies essentially; it is
607 unlikely that the drug can be repositioned in cancer therapy. However, it can open the door to the use and
608 development of other BBIQ, such as tetrandrine from *Stephania tetrandra* Radix which is perhaps a more
609 promising anticancer agent than CEP (Liu et al., 2016b; Bhagya and Chandrashekar, 2018). CEP itself could
610 be used more largely for the treatment of cancer-related conditions such as xerostomia, anemia or
611 leukopenia.

612

613 New horizons for CEP have been evoked in this review, such as a repositioning for the treatment of bone
614 disorders in particular osteoporosis. It really makes sense because NFκB is a robust therapeutic target in
615 inflammatory-associated bone diseases (Lin et al., 2017). CEP activates AMPK by targeting NFκB to suppress
616 autophagy. As such, the drug could also be considered to prevent the development of pulmonary arterial
617 hypertension (Zhai et al., 2018). Other therapeutic perspectives can be proposed. As a well-tolerated, orally
618 available inhibitor of NFκB-mediated inflammation, CEP certainly merits further investigation for efficacy in
619 clinical trials for disorders characterized by inflammation and membrane injury molecular pathways. In
620 particular, CEP might be considered for the treatment of Duchenne muscular dystrophy (DMD) which is a
621 neuromuscular disorder causing progressive muscle degeneration. In DMD, NFκB is activated and drives
622 inflammation and muscle degeneration while inhibiting muscle regeneration. The absence of dystrophin
623 makes skeletal muscle more susceptible to injury, resulting in breaches of the plasma membrane and
624 chronic inflammation in DMD. Novel NFκB inhibitors are currently evaluated as new treatments for DMD
625 patients. It would also make sense to evaluate the potential of CEP in this indication, and in other chronic
626 inflammatory diseases. Along the same vein, CEP might be useful to limit the progression of osteoarthritis,
627 a chronic degenerative joint disease incredibly prevalent in older age. CEP would not repair the already
628 degraded cartilage, but the drug might avoid damage extension to the surrounding tissue, by limiting the
629 production of pro-inflammatory cytokines and chemokines (Herrero-Beaumont et al., 2019). In particular,
630 osteoarthritis patients suffering from a cancer and treated with a regulator of the PD1/PDL1 immune
631 checkpoint might face an aggravation of their osteoarthritis due to a treatment-induced elevated
632 expression of inflammatory cytokine in macrophages (Liu et al., 2019). The use of CEP might thus be useful
633 to limit osteoarthritis progression. A new life for an old drug? Maybe. CEP is not a « one pill fits all »
634 medication but certainly an under-explored drug which should be reconsidered. Hopefully this review will
635 contribute to the renaissance of this well-established alkaloid.

636

637

638

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640

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649 contribution to **the** Figures.

650
651

652 **Figure Legends**

653 Fig. 1: Chemical structure and conformation of cepharanthine (C₃₇H₃₈N₂O₆).

654 Fig. 2: (a) *Stephania japonica* JB Koishikawa, photo of the plant leaves (Japan, 2018). (b) The caudex of
655 *Stephania rotunda* (Pierre Fabre Botanical Institute, Cambounet-sur-Sor, France). (c and d) *Stephania*
656 *cephalantha* Hayata (China), from the Paris Herbarium, at the National Museum of Natural History, Paris,
657 France (<http://coldb.mnhn.fr/catalognumber/mnhn/p/p02467444> and p02384134).

658 Fig. 3: History of CEP discovery and development. Eighty years of evolution of CEP, to mention its main
659 clinical applications and biochemical properties.

660 Fig. 4: Structure of six bisbenzylisoquinoline (BBIQ) derivatives.

661 Fig. 5: Pharmaceutical sales of CEP for years 2014-2018 (from IMS Health, now IQVIA). The graph shows
662 both the annual sales in k€ (left axis) and in k-units (right axis). Numbers for year 2018 are estimates based
663 on the June 2018 MTA (Moving Annual Total) data.

664 Fig. 6: Main signaling pathways and sites of action of CEP in cells. The multifaceted mechanism of action of
665 CEP leads to several clinical applications (treatment of **s**nake bites, alopecia aerata, xerostomia,
666 leukopenia). Other potential applications of CEP are also explored for the treatment of cancer,
667 osteoporosis, virus and parasites infections, sepsis and chronic inflammatory diseases.

668 Table 1. Bisbenzylisoquinoline (BBIQ) alkaloids

669
670

671 **Conflict of interest**

672

673 I confirm that there are no known conflicts of interest associated with this publication and there has been
674 no significant financial support for this work that could have influenced its outcome.

675

676

677 **References**

678

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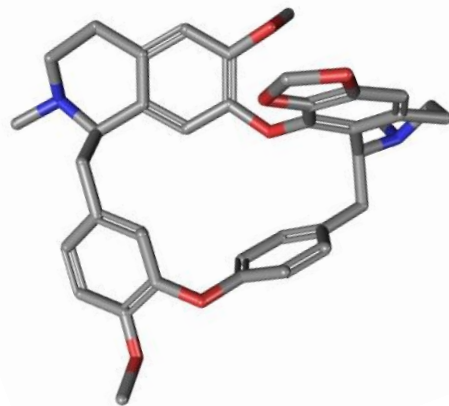
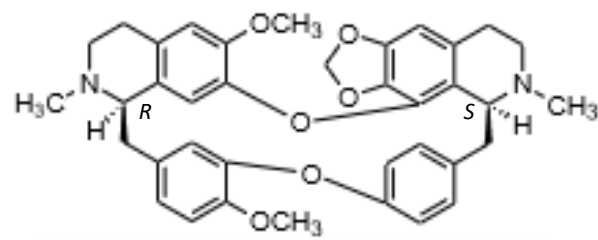


Figure 1
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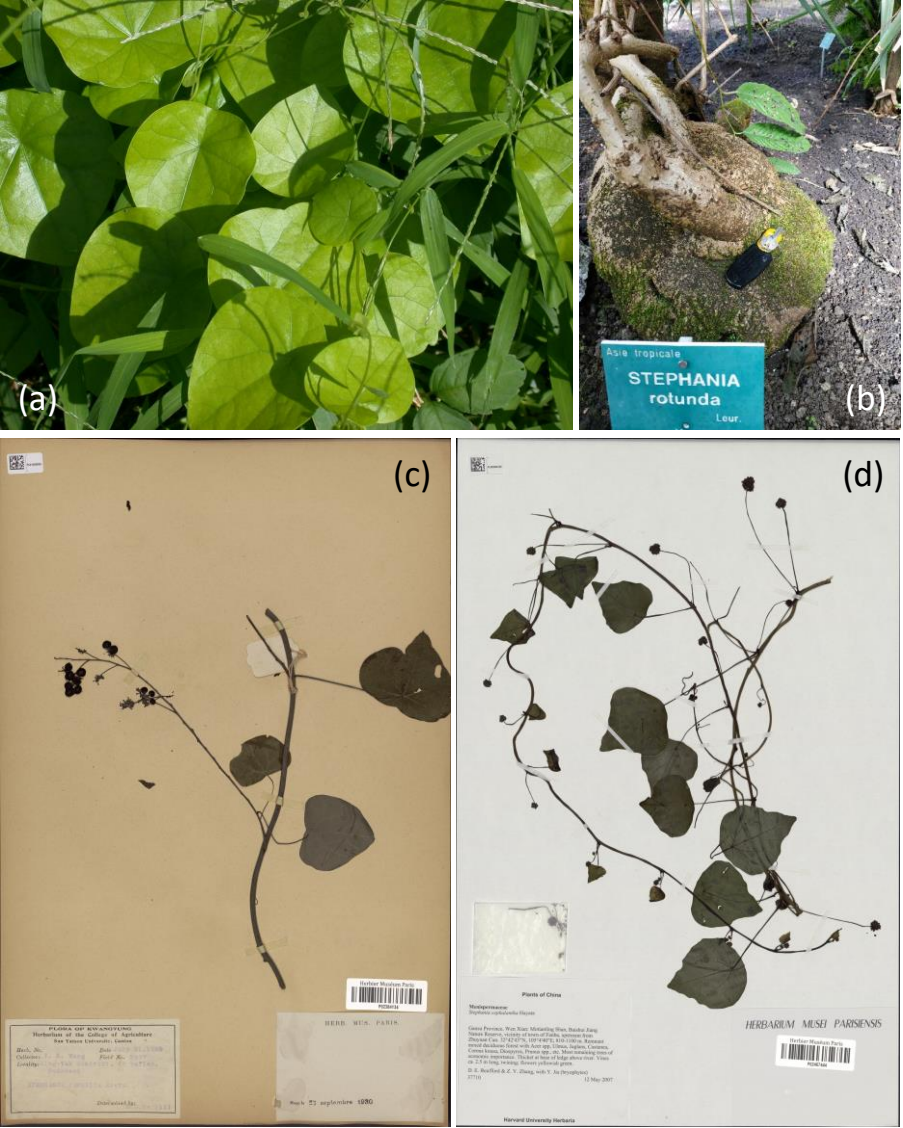


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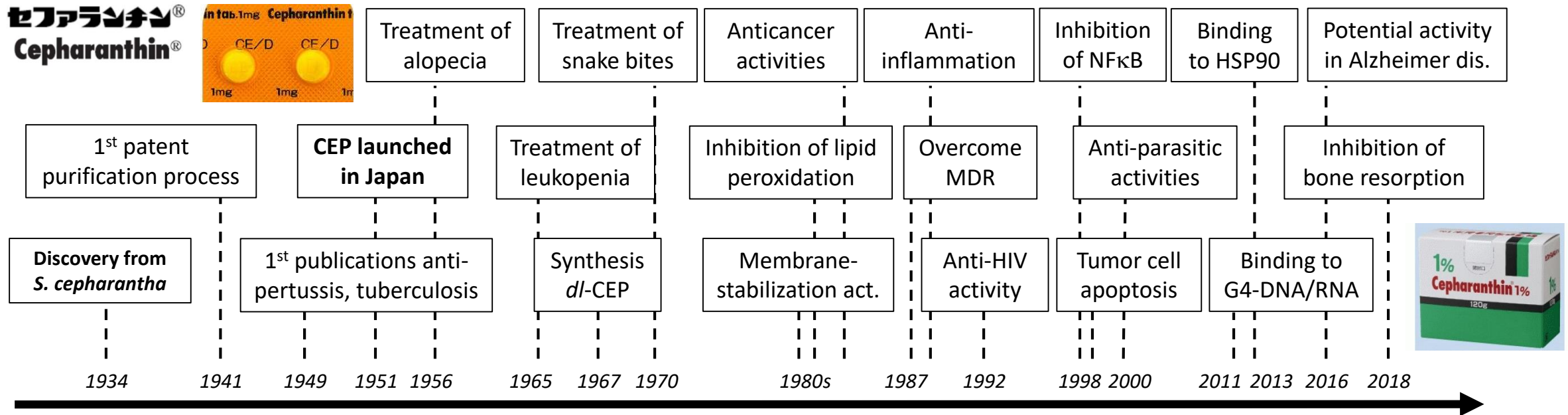
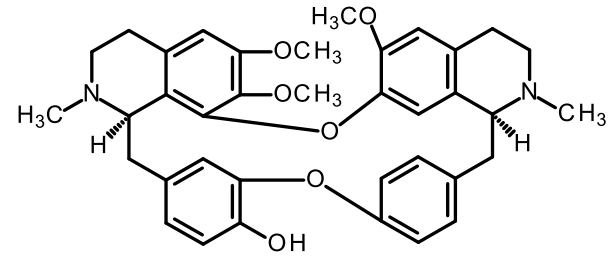
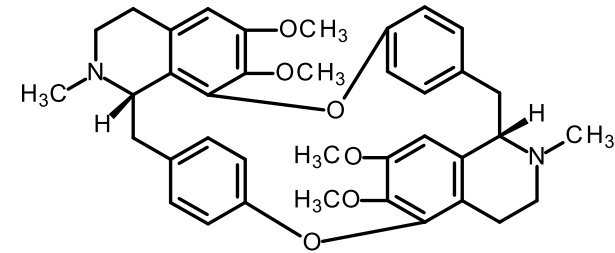


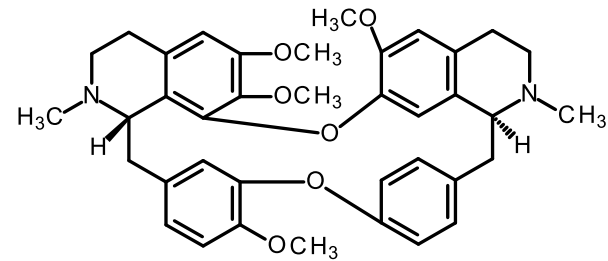
Figure 3
PHYMED-D-19-00593



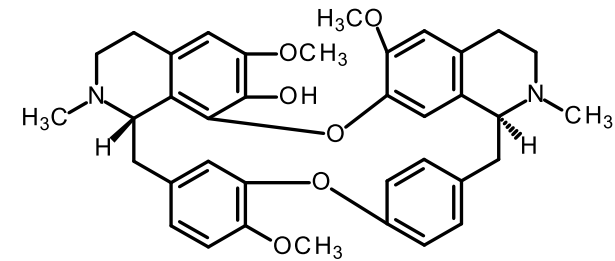
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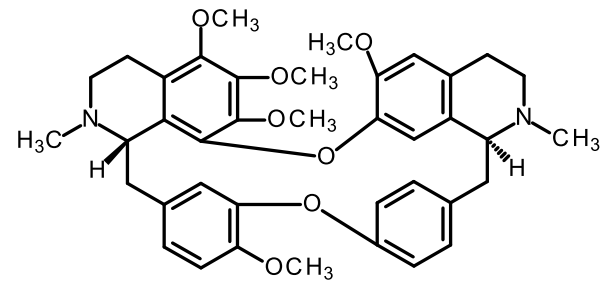
Cycleanine



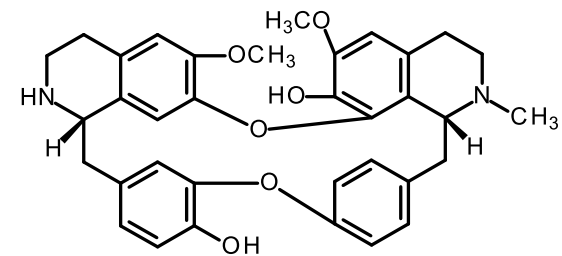
Tetrandrine



Fangchinoline



Hernandezine



Daphnoline

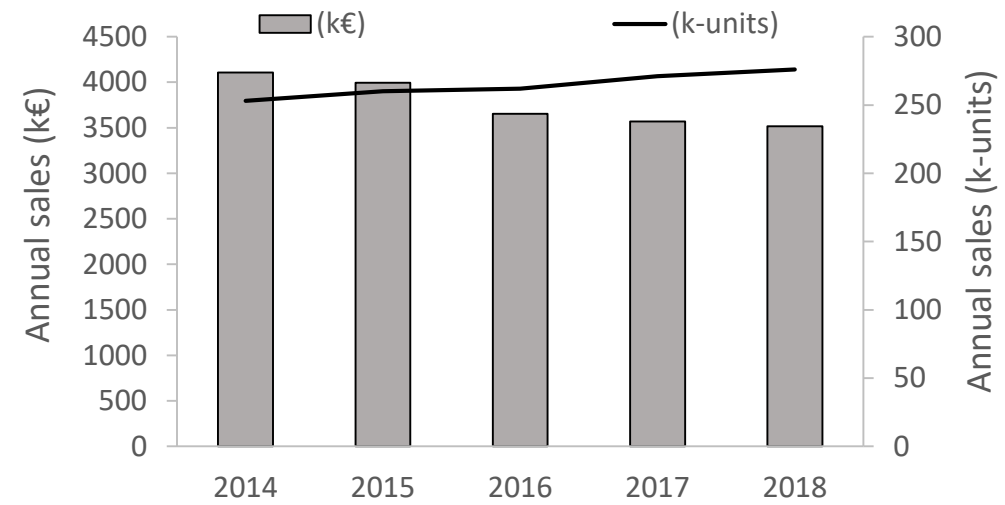
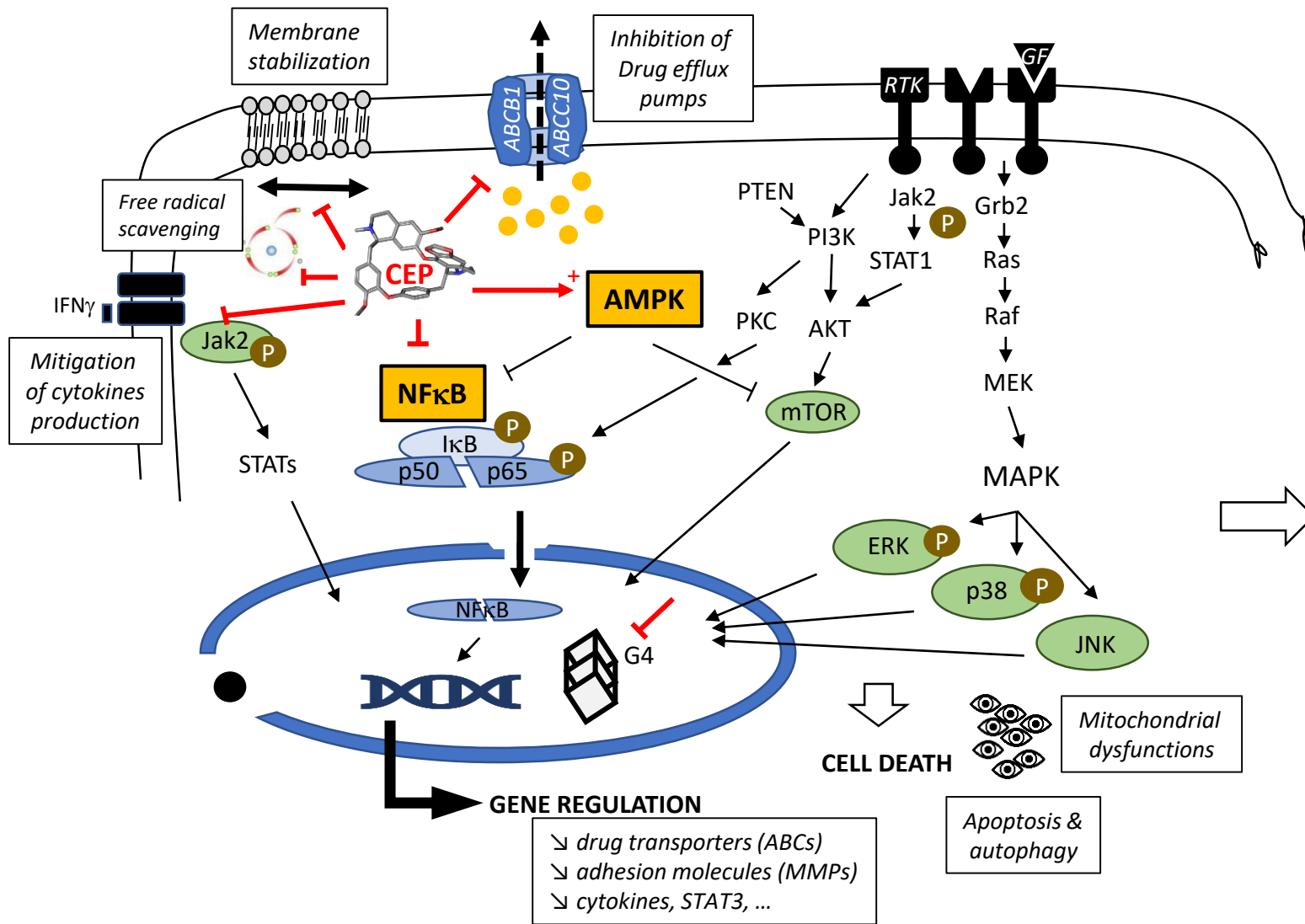


Figure 5
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Current clinical applications



Exploratory studies

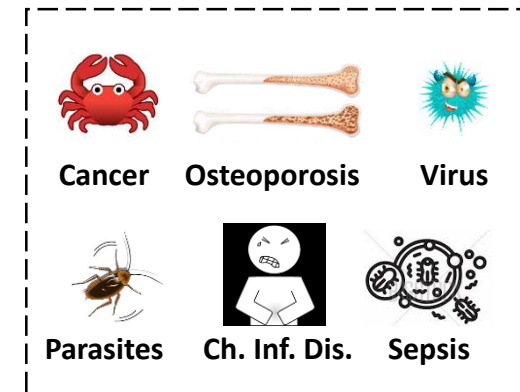


Figure 6
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1 Table 1. Bisbenzylisoquinoline (BBIQ) alkaloids

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Main BBIQs	Plants	Citations*	References
5 Tetrandrine	<i>Stephania tetrandra</i>	910	[Liu et al., 2016b]
6 Cepharanthine	<i>Stephania cephalantha</i> , <i>S. rotunda</i>	331	
7 Berbamine	<i>Berberis amurensis</i> , <i>B. vulgaris</i> , 8 <i>B. libanotica</i> , <i>B. aristata</i> , 9 <i>Rhizoma Coptidis</i> , <i>Rhizoma Coptis</i>	188	[Zhu et al., 2018]
10 Neferine	<i>Nelumbo nucifera</i> , <i>Plumula nelumbinis</i>	141	[Marthandam Asokan et al., 2018]
12 Fangchinoline	<i>Stephania tetrandra</i>	115	[Mérarchi et al., 2018]
13 Dauricine	<i>Menispermum dauricum</i>	110	[Liu et al., 2018c]
15 Other BBIQs		352	[Barbosa-Filho et al., 2000; Weber and Opatz, 2019]
18 antioquine, aromoline, baluchistine, berbicolorflammine, berbibuxine, calafatimine, cocsoline, cocsulinine, colorflammine, curacautine, curine, cycleahomine, cycleanine, cycleatjehine, daphnine, daphnoline, daurisoline, dihydrosecocepharanthine, dihydrothalictrinine, faralaotrine, funiferine, gillette, hernandezine, johnsonine, krukovine, liensinine, limacine, limacusine, macolidine, macoline, malekulatine, norpanurensine, obaberine, oblongamine, osornine, oxandrine, phaeantharine, racemosidine, repandine, sinomenine, temuconine, thalbadenzine, thalfine, thalibrunine, thalictine, thalictitrine, thalidasine, thalidezine, thalmethine, thalmine, , tiliageine, tubocurine			

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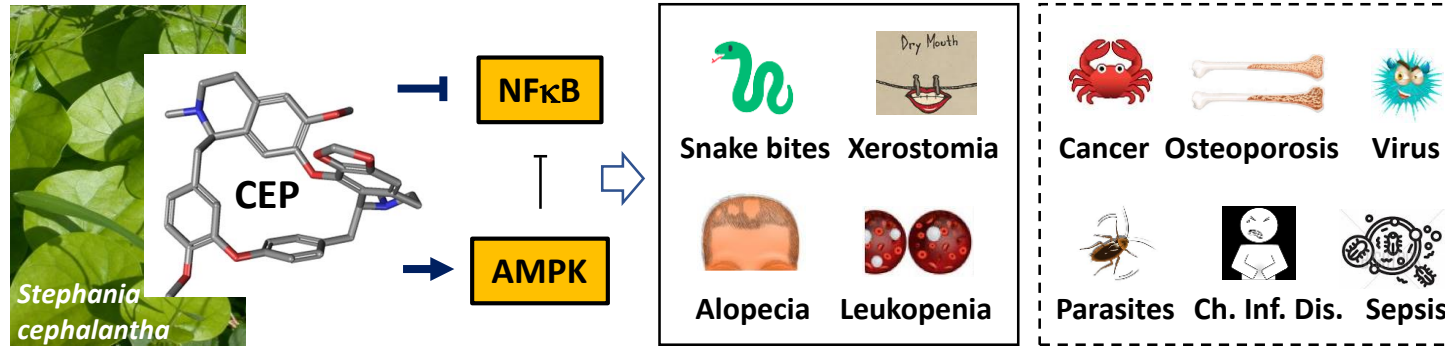
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26 (*) Number of citations in the PubMed database (May 2019)

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Revised Graphical Abstract

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Ch Bailly