ASIAN JOURNAL OF PHARMACOGNOSY
Asian J. Pharmacogn 2(3):22-31
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eISSN-0128-1119

Cryptosporicidal Activity of Plant Extracts against *Cryptosporidium parvum* and *Cryptosporidium hominis*

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Received May 20, 2018; accepted May 25, 2018; published online June 10, 2018

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ABSTRACT

Cryptosporidium spp., an obligate epicellular coccidian that causes cryptosporidiosis, is a neglected parasite. There are 26 known species of *Cryptosporidium spp.* as recognized by host specificity, morphology, and molecular biology studies but only two of them infect humans - *Cryptosporidium parvum* and *Cryptosporidium hominis*. This review evaluates the cryptosporicidal effects of plant extracts against *C. parvum* and *C. hominis*. Established studies showed that 8 plants have shown potential cryptosporicidal effects; blueberry with its polyphenolic compounds, cinnamon with its phenolic compounds and onion with its flavonoids and sulfide compounds, garlic with its allicin, mango with its mangiferin, olive pomace with its oleuropein, pomegranate with its polyphenols and tannins, and oregano with its carvacrol. Since the only approved medicine against *Cryptosporidium spp.* is Nitazoxanide, these promising results may allow us to discover novel drug compounds against *Cryptosporidium spp.*, especially *C. parvum* and *C. hominis*. Furthermore, the results are still suggested for further studies and improvement in order to enhance the knowledge we have gathered of the bioactive compounds of the said plants against these pathogenic species of parasite.

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Keywords: *Cryptosporidium*; cryptosporidiosis; neglected parasite; cryptosporicidal effects.

INTRODUCTION

Cryptosporidium is an obligate epicellular apicomplexan. (Thompson, et al. 2016). *Cryptosporidium spp.* are also known as gastrointestinal protozoan parasites that cause mainly enteric

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eISSN-0128-1119

illnesses in humans and other animals but was only initially thought to cause disease in animals (Borowski, et al. 2010). *Cryptosporidium spp.* infect a range of animals, which also includes humans. *Cryptosporidium parvum* and *Cryptosporidium hominis* are considered to be the most prevalent as they are pathogenic. Along the years, cases about the human infections of *Cryptosporidium felis, Cryptosporidium meleagridis, Cryptosporidium canis,* and *Cryptosporidium muris* have been reported (Shapiro, 2012).Cryptosporidiosis is the term used to describe the infection caused by the zoonotic pathogen *Cryptosporidium parvum* and the anthroponotic pathogen *Cryptosporidium hominis* (Hashim, et al. 2006). Most cases of cryptosporidiosis in humans are self-limited but can be devastating in immunocompromised individuals especially in children and infants living in underdeveloped countries. There are two major reasons why the parasite continues to be a major threat to human health. First, the present water purification methods are ineffective in removing the said parasite from public water supplies. Second, there is no proven effective therapy for cryptosporidiosis (Leav, et al. 2003).This review covers the collected knowledge regarding the natural extracts of different plant species that showed activity against *Cryptosporidium spp*. The eight plant species have been extensively studied and has been proven by the collected data as a possible source of treatment for Cryptosporidiosis. Cryptosporidium can be found in water, soil, or surfaces that was contaminated with feces from infected animals or humans (Putignani and Menichella, 2010). Cryptosporidium was first described in the early 20th century. The first species described were *Cryptosporidium muris* and *Cryptosporoidium parvum* but the economically important cause of neonatal diarrhea in calves and lambs is regarded by *C. parvum* (Hunter, et al. 2013). In 1910, the genus *Cryptosporidium* was proposed by Tyzzer when he frequently found that it is infective in mice specifically in the gastric glands of laboratory mice. The organism completed its life cycle in a single host within the epithelial cells in the intestine, underwent both sexual and asexual development, and as a result produced an oocyst that was excreted in the feces of the mouse (Rose, 1997). In 1976, cases of human cryptosporidiosis were reported in patients with severe watery diarrhea. This has led to a laboratory diagnosis of cryptosporidiosis possessing various symptoms such as diarrhea and abdominal pain. During the early 1980s, AIDS patients led to the inclusion of cryptosporidiosis in which they are identified through chronic infections and mortality rates. Cryptosporidium infections are identified to have two modes of transmission - the indirect and direct transmissions. Zoonotic and anthroponotic are considered to be the direct transmission for the said infection. Institutions where the spreading of infections are transmitted person to person can become outbreak settings while animal to human transmission of cryptosporidiosis comes from outbreaks of infected young calves that had contact with veterinary students and researchers. Indirect transmissions include contact with Cryptosporidium that came from contaminated water, food, fomites and through environmental contamination from release of feces, sewage or wastewater that can be overflow following heavy rain events. Immunocompromised patients can be infected through the inhalation of oocysts which can be another mode of transmission that could be accompanied by mild diarrhea and respiratory infections as symptoms (Hunter, et al. 2013).Cryptosporidium infection is probably underdiagnosed as a cause of community-acquired diarrhea as there have been occasional outbreaks of infection in daycare centers, foodborne outbreaks, and outbreaks associated with recreational water such as public swimming pools, lakes, and ponds. The largest outbreak occurred in 1993 at Milwaukee where the majority of reported cases of cryptosporidiosis in humans have been associated with contaminated drinking water (Leav, et al. 2003). Although cryptosporidiosis is a significant cause of diarrheal disease in both developing and industrialized countries, some epidemiological studies have shown that Cryptosporidium is more common in developing countries (5% to >10%) than in developed countries (<1%–3%) This protozoan infects children under 5 years of age due to diarrhea that is thought to be responsible for 30–50% of childhood mortality in developing countries (Mahmouidi, et al. 2017).

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eISSN-0128-1119

Cases of *Cryptosporidium hominis* has been recorded around the world since its discovery (Morgan-Ryan, et al. 2002). Several outbreaks were reported in different areas such as the United States, England, Japan and other countries worldwide (Xiao and Feng, 2008). *C. parvum* has been usually the primary cause of infection in Europe but *C. hominis* has seen a significant increase in cases as they are more prevalent in areas such as South America, Australia, and Africa (Chako, et al. 2010). Incidence were prevalent in North and South America, Australia, and Africa. They are also observed in developing countries such as Peru, Malawi, Kenya, Haiti, India, Brazil, South Africa, and Uganda. *Cryptosporidium parvum* is recorded to be prevalent in European countries especially in the United Kingdom. Also, *Cryptosporidium parvum* is observed in other countries such as Peru (Putignani and Menichella, 2010). *Cryptosporidium* is a microscopic parasite and considered as one of the most common food and waterborne diseases acting as a common cause of diarrhea in animals and man (Latif and Rossle, 2013). *Cryptosporidium* meaning a "hidden spore", (Parlange, 1999) the cyst stage of this parasite, which is resistant to chlorine disinfection used in pools, can survive for long period of time in the environment due to its outer shell that protects and allows it to survive outside the body. *C. parvum* and *C. hominis* are transmitted primarily through contact with contaminated water. (Kelly and Lloyd, 2013). Zoonotic and anthroponotic transmission of *C. parvum* and *C. hominis* occur through contact with water, contaminated by feces of infected animals or exposure to infected animals itself. Excystation occurs after being ingested, or even inhaled, by an acceptable host (Putignani and Menichella, 2010). The release of sporozoites parasitizes epithelial cells of the gastrointestinal tract or other tissues such as respiratory tract. The parasite undergoes asexual then sexual multiplication (schizogony or merogony, and gametogony respectively) producing microgamonts and macrogamonts. When the macrogamonts are fertilized by the microgametes, oocysts develop that sporulate in the infected host. A thick-walled and thin-walled oocysts are produced that are primarily involved in autoinfection. Upon excretion, the oocyst are infective therefore allowing direct fecal-oral transmission (Laurent, et al. 1999). *C. hominis* is almost exclusively a parasite of humans while *C. parvum* has a broad host range. Therefore, *C. hominis* has a low zoonotic potential compared to *C. parvum*. It is spread through the fecal-oral route usually by drinking water contaminated with oocyst laden feces (Shapiro, 2012).

There are two factors that are said to be important in relation to the survival time of the oocyst, the temperature and the solar radiation both can increase and decrease the survival of oocyst (Lindgren, 2015). Multiple mammalian species can be infected by *C. parvum* and has a significant impact both on domestic farm animals and human health (Peng, et al. 1997) while humans and monkeys are the major hosts of *C. hominis* (Caccioa, et al. 2005). It was found present in a number of calves in the UK, USA, Australia, and India, though extremely rare. (Xiao and Feng, 2008). Nitazoxanide is the only drug that has been licensed by the Food and Drug Administration for the treatment of diarrhea associated with cryptosporidiosis from age 1 year or older. It is a thiazolide antiparasitic agent that shows excellent activity against a wide variety of protozoa and is derived from nitrothiazolyl-salicyamide (Fox and Saravolatz, 2005). Although less effective, another drug for its treatment is paromomycin. Paramomycin possesses the ability to ameliorate the cryptosporidiosis in AIDS patients but studies suggested that Nitazoxanide provides a better response towards the said disease. There are cases where combinations of drugs were used to treat cryptosporidiosis. Examples of these would be nitazoxanide-fluoroquinolone, nitazoxanide-azithromycin, and paramomycin-azithromycin drug combinations. Rifabutin-nitazoxanide combination also proved to be a promising treatment for cryptosporidiosis. Azithromycin, spiramycin, and bovine anti-cryptosporidium immunoglobulin are the drugs that are reported to have some effect against cryptosporidiosis but still

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eISSN-0128-1119

ineffective when it comes to treating patients with AIDS (Sparks, et al. 2015). Higher levels of virulence indicate a higher priority of treatment that is why different sources of novel anti-parasitic compounds must be utilized. The use of medicinal plants for the treatment of parasitic diseases has been documented since ancient times. One of the most rewarding frontiers in modern science is the study of the chemistry and biology of natural products as it can lead to the discovery of untapped natural sources of novel antiparasitic compounds (Kayser et al. (2002).

MATERIAL AND METHODS

The research study was conducted using electronic literature review methods. In this review, published studies and literature were collected from PubMed, Science direct, Google Scholar, and Elsevier for the cryptosporicidal effect against *Cryptosporidium parvum* and *Cryptosporidium hominis*. These published articles were then appraised for their anti-parasitic activities. Among these, activities of natural plant products were observed showing various effects on different parts of *Cryptosporidium spp*.

RESULTS AND DISCUSSION

A total of 10 published studies were collected to provide an overview of the plants that exhibited potential cryptoporicidal activity. These plants are *Vaccinium myrtillus* (blueberry), *Cinnamomum zeylanicum* (Cinnamon), *Allium sativum* (Garlic), *Mangifera indica* (Mango), *Olea europaea* (Olive Pomace), *Allium cepa* (Onion), *Punica granatum* (Pomegranate), and *Origanum vulgare* (Oregano). The data collected was presented by stating the studied plant part, the identified active component, the organism being targeted, and the observed activity and effect of the said active component. (Refer to Table 1). Also, the procedure and findings of the published studies for each plant was summarized in order to compare the cryptosporicidal activities that they have exhibited.

Blueberry

Spontaneous excystation of *Cryptosporidium parvum* oocysts using pressed blueberry extract, Bouvrage beverage, and the polyphenolic-rich blueberry extract were investigated in a study that showed the effect of various preparations of blueberry (*Vaccinium myrtillu*s) extract on *C. parvum* oocysts. Spontaneous excystation includes two possible therapeutic benefits. The first is the release of *Cryptosporidium parvum* sporozoites in the acidic environment of the stomach, which leads to their premature lysis and the second is the increased excystation in the intestine leading to a reduction in the excretion of infectious oocysts. The spontaneous excystation of *C. parvum* oocysts is increased at 37 °C by the extracts of pressed blueberry, Bouvrage beverage, and polyphenolic-rich blueberry. The spontaneous excystation have increased only at the dilution level of 50% Bouvrage beverage, which is equivalent to 213 μg/mL gallic acid equivalents in the polyphenolic-rich blueberry extract. Once the level had exceeded, the spontaneous excystation is decreased. The study suggests that modification of parasite morphology and reduction or inhibition of lectin-mediated attachment to enterocytes for the effects of water-soluble extracts of blueberries occur on enteropathogenic protozoa (Anthony, et al. 2007).

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Table 1. Summary of cryptosporicidal activity of various plants

PLANT	PART	ACTIVE COMPONENT	TARGET ORGANISM	OBSERVED EFFECTS	MINIMUM CONCENTRATION OF INHIBITION	REFERENCES
Blueberry (*Vaccinium myrtillus)*	Fruit	Polyphenolic compounds	*Cryptosporidium parvum*	Increases the spontaneous excystation leading to the reduction of *C. parvum* oocysts.	213µg/ml	Anthony et al., 2007
Cinnamon (*Cinnamomum zeylanicum)*	Bark	Phenolic compounds	*Cryptosporidium parvum*	Induces a significant reduction in oocysts count of *C. parvum*	1 ml/100g	Abu El Ezz et. al., 2011 Ranasignhe et. al., 2013
Garlic (*Allium sativum)*	Bulb	Allicin	*Cryptosporidium spp.*	Decreases the number of cryptosporidial oocysts and disrupts the normal physiological functions of the parasite.	50 mg/kg	Gaafar,2012 Masamha et. al., 2010
Mango (*Mangifera indica)*	Leaves	Mangiferin	*Cryptosporidium parvum*	Exhibits high percentage reduction of *C. parvum* colonies.	100 mg/kg	Shah et al., 2010 Perrucci et al., 2006
Olive Pomace (*Olea europaea)*	Leaves	Oleuropein	*Cryptosporidium parvum*	Reduces *C. parvum* colonization.	15 mg/kg	Khater et. al., 2017
Onion (*Allium cepa)*	Bulb	Flavonoids and sulphoid compounds	*Cryptosporidium parvum*	Induces a significant reduction in oocysts count of *C. parvum*	1 ml/100g	Abu El Ezz et. al., 2011
Pomegranate (*Punica granatum)*	Peel	Polyphenols and tannins	*Cryptosporidium parvum*	Eliminates oocyst shedding and reduces C. parvum trophozoites and lymphatic infiltration.	3 g/kg	Al-Mathal et. al., 2012
Oregano (*Origanum vulgare)*	Leaves	Carvacrol	*Cryptosporidium parvum*	Blocks the growth and development of *C. parvum.*	30µg/ml	Gaur et al.,2018

Cinnamon and onion

Various sources have reported pharmaceutical activity of extracts of *Allium cepa* and cinnamon oil including anti-microbial and anti-parasitic activity. Researchers have investigated the effect of administration of onion (*Allium cepa*) and cinnamon (*Cinnamomum zeylanicum*) oils on the growth and advancement of the experimental cryptosporidiosis in mice. Each mouse was experimentally infected

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eISSN-0128-1119

with 10^6 *Cryptosporidium parvum* oocyst. After the establishment of infection, infected mice of G1 and G2 were given a dose of 1ml/100g body weight of onion and cinnamon orally. The G3 mice were control positive while the G4 mice were control negative. Fecal smears from mice were examined daily for 17 days as a post-treatment. Oocyst count and mucosal histology were assessed for experimentally infected mice. The two oils showed an effect on oocysts shedding, although there was no complete elimination of the parasite and induced a significant reduction in oocysts count of *Cryptosporidium parvum*. The anti-parasitic effect of the two oils were due to the presence of flavonoids and sulfide compounds in the bulbs of *Allium cepa* and the presence of phenolic compounds in the bark of cinnamon. (Ranasinghe, et al. 2013) *A. Cepa* oil was found to be more effective in comparison with *C. zeylanicum*. It was concluded that administration of onion or cinnamon oils was beneficial in protecting susceptible hosts against opportunistic parasites such as *Cryptosporidium spp.* (Abu El Ezz, et al. 2011).

Garlic

Garlic has been reported to have antimicrobial, antihelminthic, anti-coccidiosis, and anti-cryptosporidiosis activities. *A. sativum* is attributed to allicin which is one of the organosulfate compounds found in the bulbs. It is responsible for the anti-microbial properties and the characteristic flavor of fresh garlic. According to a study, forty-eight male Swiss albino mice were divided equally into control and experimental groups. Each group was further subdivided into four equal subgroups; two immunosuppressed and two immunocompetent. Results show that the infected immunosuppressed subgroups of mice showed a statistically significant increase in the number of cryptosporidium oocysts in stool and ileal sections, as well as an increase in the MPO (Myeloperoxidase) activity when compared to the corresponding immunocompetent subgroups. Increase in MPO activity level is an indicator of intestinal inflammation. Garlic successfully eradicated the Cryptosporidium oocysts from the stool and intestinal sections of the infected immunocompetent subgroup of mice receiving garlic two days before the infection. Besides, the oocysts were significantly reduced in all other infected experimental subgroups in comparison to the corresponding infected control subgroups. The intestinal sections of all subgroups received garlic before or after the infection, revealed a more or less normal architecture. Reduction in the level of MPO activity was also detected in all experimental subgroups. The study concludes that garlic is a convenient prophylactic and a promising therapeutic agent for cryptosporidial infection (Gaafar, 2012). Furthermore, a study reported that *A. sativum*, disrupts the normal physiological functions of parasite mobility, food absorption and reproduction (Masamha, et al. 2010).

Mango

Studies show that mango possesses anti parasitic property. The bioactive compound found in *Mangifera indica* is called Mangiferin (Shah, et al. 2010). A study about the inhibitory activity of mangiferin (50 mg/kg/die and 100 mg/kg/die) on *Cryptosporidium parvum* was evaluated in a neonatal mouse model and its activity was compared with that of paromomycin (100 mg/kg/die). Results obtained show that mangiferin at 100 mg/kg/die has a significant anticryptosporidial activity and this activity is similar to that showed by the same dose (100 mg/kg/die) of paromomycin. However, both mangiferin and paromomycin were not able to completely inhibit intestinal colonization of *C. parvum* but only to reduce it. This reduction was calculated at over 80% for both mangiferin and paromomycin with respect to the untreated control. Though there was a high


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eISSN-0128-1119

percentage of reduction in colony, mangiferin only reduced the colony and was not able to completely inhibit the intestinal colonization of *C. parvum* (Perruci, et al. 2006).

Olive Pomace

Olea europaea is well-known to possess anti-inflammatory and antioxidant effects. Researchers have studied *Olea europaea* in order to know the said fruit's potential to exhibit anti-parasitic property. In their study, neonatal mice were experimentally infected to evaluate the anti-Cryptosporidium therapeutic capability of *Olea europea* by detecting of *Cryptosporidium parvum* oocysts and copro-DNA, using microscopy and nested PCR assay, as well as histopathological examination of their small intestine. Intragastric inoculation of *C. parvum* oocyst was performed to infect the Swiss albino mice with *Cryptosporidium* and after 3 days of infection, infected mice were given an oral dose of 15mg/kg from *O. europaea*. After 2 weeks of drug administration, there was a 100% reduction of *Cryptosporidium* oocyst excretion in stool and copro-DNA of *O. europaea*-treated infected mice. The anti-parasitic effect of olive pomace was due to the presence of oleuropein, which is the main constituent of *O. europaea* leaves. Upon the results, *O. europaea* possesses a promising effect on intestinal cryptosporidial infection that could be employed as a natural, safe product for the readying of a novel therapeutic agent. Nevertheless, it will be necessary to isolate and purify the bioactive components of OLE, and such result could be adapted in similar infections in animals or even man (Khater, et al. 2017).

Pomegranate

A study shows that pomegranate possesses anti-parasitic activities. They evaluated the effect of *P. granatum* peels on neonatal albino mice infected with experimental *C. parvum* by oral administration of *C. parvum* oocysts. On post-inoculation, aqueous suspensions of *P. granatum* peel (3g/kg body weight) were received by treated mice orally. Examination of parameters such as the presence of diarrhea, oocyst shedding, and weight gain/loss, and the histopathology of ileal sections were performed and have shown improvement. Infected mice that were treated with *P. granatum* peel suspension showed continuous weight gain, improved intestinal histopathology, oocyst shedding was completely eliminated; *C. parvum* trophozoites and lymphatic infiltration were significantly reduced. Further, these mice did not exhibit any clinical symptoms and no deaths have occurred. The anti-parasitic effect of pomegranate may be due to the powerful anti-oxidants and anti-inflammatory substances that include polyphenols and tannins in the peels of the fruit. These results suggest that *P. granatum* peels are an effective treatment for *Cryptosporidium parvum*-induced cryptosporidiosis that lacks negative side effects (Al-Mathal and Alsalem, 2012).

Oregano

The unique biology, distinct structure, and biochemical composition of the drug-resistant properties of *Cryptosporidium parvum* are very different from other apicomplexan parasites. This resilient characteristic is due to its intracellular but extracytoplasmic shelter that creates a parasitophorous vacuole separating it from the cytosol by a feeding organelle. The study focuses on OEO (oregano essential oil) and CV (carvacrol) in countering *Cryptosporidium spp.* because the said extract and compound are acknowledged as having anti-microbial and antiparasitic activities. Due to the Monoterpenes of OEO such as CV, the calcium-dependent protein kinase 1 (CDPK1) can be modified and affect the Ca2+ mediated signaling of the parasite, which is required for invasion,


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eISSN-0128-1119

differentiation, and regulation of other vital functions. The hydrophobicity and presence of hydroxyl groups in CV and thymol may allow the phenols to penetrate the cell membrane and reduce parasitic infection by modulating cytoplasmic metabolic pathways such as ATP synthesis. *C. parvum* relies solely on the host for nutrient acquisition and for isoprenoids precursors. Isoprenoids precursors are required for prenylation, geranylgeranylation, N-glycosylation, and ubiquinone biosynthesis for parasite growth. Essential oil monoterpenes such as linalool, similar in size and structure to CV, are also reported to inhibit 3-hydroxy-3-methyl-glutaryl-Co-enzymeA (HMG-CoA) reductase, which is the key regulatory enzyme in isoprenoid synthesis via the mevalonate pathway in the host cells. The said interaction of compounds limits the acquisition of isoprenoid precursors from the host and blocks the growth and development of *Cryptosporidium spp.* (Gaur, et al. 2018).

The collected information about the cryptosporicidal activity of plant extracts against *C. parvum* and *C. hominis* showed that certain parts of the selected plants possess an active component that showed activity against *C. parvum* specifically and only garlic showed activity against the whole Cryptosporidium genus. The active compounds from the potent plant fractions were mainly found in the bark of the plants while few of them were isolated from fruits. The active components mainly target the oocyst of Cryptosporidium thus inhibiting the growth of the parasite but the active components vary in their strength against Cryptosporidium. Although it is possible that there are other plants that may show activity against Cryptosporidium, this review may open new opportunity to test other plants based on the table given.

CONCLUSION

In conclusion, with these literature reviews, natural products isolated from these plants can be utilized as alternatives for Nitazoxanide since they showed significant or potent cryptosporicidal activities. These findings may grant us the possibility of discovering a novel drug against this neglected parasite. However, further studies and improvements are still required to attaina better knowledge of the bioactive compounds present in the plant extracts as it could allow us to maximize the effect they can produce when utilized. It is also important to continue research *Cryptosporidium spp*. to fully understand its nature and pathogenicity.

ACKNOWLEDGMENTS

The authors are grateful to the Walailak University and Centro Escolar University for providing the facilities needed to achieve this review. Our gratitude is also extended to the President of Centro Escolar University, Dr. Ma. Cristina D. Padolina, Dean of School of Science and Technology, Dr. Julieta Z. Dungca, and Head of Biological Sciences Department, Dr. Zenaida D. Los Baños for the support they have given, practicum coordinator, Dr. Alicia I. Yu, and practicum trainer, Assoc. Prof. Dr. Veeranoot Nissapatorn for their continuous assistance, and Walailak University for giving a warm welcome during the international practicum conducted at their campus. We also thank Dr. Tooba Mahboob, Mr. Giovanni de Jesus Milanez, and Assoc. Prof. Frederick Masangkay for providing a thorough understanding of the topic of this review.

DECLARATION OF CONFLICT OF INTEREST

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Asian J. Pharmacogn 2(3):22-31
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eISSN-0128-1119

No conflict of interest associated with this work.

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ASIAN JOURNAL OF PHARMACOGNOSY
Asian J. Pharmacogn 2(3):22-31
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eISSN-0128-1119

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