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REVIEW ARTICLE

A review on Using Natural Products to Prevent the Compilation of Schistosomiasis

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Abstract: Genus schistosoma is a very well-preserved parasite among millions of years. Over many decades, is responsible for the morbidity and mortality of hundreds of million humans. Effective medication (Praziquantel) for acute treatment is commercially available, and prophylaxis by vaccination is promising. Where endemic Schistosomiasis is still prevalent, causing significant morbidity and mortality have far-reaching complications in many human organ systems, including irreversible pulmonary hypertension, genitourinary, central nervous system conditions, and also neoplasia. Natural products have been the source of multiple medicines for thousands of years. The discovery of pure compounds as active ingredients in plants was first described at the beginning of the 19th century. Natural products have come from variable source materials including terrestrial microorganisms, terrestrial plants, marine organisms, and terrestrial invertebrates and vertebrates. The use of drugs extracted from bacteria, fungi, plants, and marine organisms has a long common and tradition in medicine. Among these, medicinal plants include variable active principles that have been exploited against schistosomiasis syndrome, and in recent decades, natural products have attracted worldwide interest.
Keywords: Schistosomiasis, Natural products, Allicin, Curcumin, Garlic, Nigella sativa

1 | INTRODUCTION

Schistosomiasis affects an estimated 240 million people are affected in 78 countries, (Butrous, 2019). Schistosomiasis pathogenicity can cause acute and chronic clinical syndromes (Coltart and Whitty, 2015; Bonnefond et al., 2019). It was approved that schistosomiasis can cause changes in hematological parameters, the elevation of oxidative stress represented

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in lipid peroxide with diminishing in antioxidant's factors (Sorgho et al., 2017; Jatsa et al., 2018; El-khadragy et al., 2019). At the molecular level, scientists found that Schistosoma is a harmful genotoxic agent (Madbouly et al., 2007; Abdel-Wahhab et al., 2017, Abdalkareem and Yin, 2019).

Investigators recorded that praziquantel (PZQ) efficacy, the drug of choice, had been reduced as anti-schistosomal (Crellen et al., 2016; Woldegerima et al., 2019). Schistosomiasis still searches for antiparasitic drugs from the natural origin for the development of new medications (Simões et al., 2015; Selem et al., 2018; Acheampong et al., 2020).

Allicin (AL) is the main active ingredient of Allium sativum (commonly known as garlic) and was considered responsible for many of the beneficial effects associated with this plant (Borlinghaus et al., 2014). Most of the in vitro and in vivo studies dealt with garlic itself or its aqueous or oil extracts as a medication of S. mansoni (EL-Shenawy et al., 2008; Metwalley, 2015; Sadrefozalayi et al., 2018).

Curcumin (CU), the active ingredient of Curcuma longa is a naturally basic phenolic compound produced as a yellow pigment from turmeric which was generally used as a spice and food colorant (Buescher and Yang, 2000). It was reported that C. longa extract had an antischistosomal effect which was proved by histological, physiological, and molecular applications (Aboueldahab and Elhussieny, 2016). The aim of the review was to point out the difference between the drug and the natural product in the treatment of schistosomiasis.

1. Schistosomiasis

Schistosomiasis is a parasitic disease that is historically known as bilharzia resulted from the trematode of the genus Schistosoma. Estimates place the affected all over the world population for all forms of schistosomiasis at 230 million, with about 700 million at risk (Tan, 2007). The schistosome life cycle includes two hosts: snails and mammals. Asexual reproduction happens in freshwater snails; Biomphalaria alexandrina for S. mansoni and Bulinus truncates for S. haematobium. In the snail, this starts with the transformation of miracidia into a sporocyst. Sporocysts then multiply and grow into cercariae. In the mammalian hosts, parasites grow to become mature, mate and finally produce eggs (Mouahid et al., 2018; Viana et al., 2018).

In acute schistosomiasis, most people do not develop symptoms. Although symptoms usually resolve after a few weeks, mortality rates can be as high as 25% during this acute stage. A maculopapular rash appears at the site of infection (penetration of schistosomula) (Nour, 2010).

In the chronic stage, symptoms can observe months or years later. They vary based on the species that has infected the host. In general, the eggs induce a marked immune response and form granulomas. S mansoni and S japonicum resulted in abdominal pain, bloody diarrhea, and colonic polyposis. in chronic inflammation with fibrosis and, severe organ damage, such as ureteral obstruction, squamous bladder cancer, genital lesions in the case of Schistosoma haematobium, while causing periportal fibrosis with portal hypertension in both Schistosoma mansoni and Schistosoma japonicum (Colley et al., 2014).

2. Using the drug in the treatment

Scientists still searching for antiparasitic drugs from natural origin, mainly from plants, which are the main source of biologically active ingredients for the development of new medications (Magalhães et al., 2009; Silva et al., 2009). Traditional medicinal plants were utilized by some authors for the treatment of schistosomiasis (Soliman, 2012; Sheir et al., 2015; Wangchuk et al., 2016; Al-Kazzaz, 2018).

3. Using the natural product in the treatment

Most of the old studies have focused on studying the effect of the plant itself as an extract on different helminths (Sparg et al., 2000; Molgaard et al., 2001) but the more modern studies especially those in the last 10 years focusing on the effective ingredients (Metwally et al., 2018

were applied. The great development in biochemical and analytical methods over the past 10 years allowed the separation of plant phytochemicals and consequently analysis of their chemical nature.

3.1 The active ingredient of Allium sativum

Since ancient times, garlic has been utilized all over the world, as a food and also as a treatment. In ancient civilizations, including Egyptian, Phoenicians, Greek, Indian, Roman, Babylonian, Viking, and Chinese, garlic was used as a medication for different disorders including heart conditions, arthritis, pulmonary diseases, respiratory infections, skin disease, symptoms of aging, diarrhea, headache, different bites, worms, wounds, ulcers, and multiple tumors (Rivlin, 2001).

Garlic (A. sativum), has an outstanding protection system, consisting of many different ingredients the same as in the human immune response. To protect itself from invaders as insects and fungi, garlic produces AL by the enzymatic reaction when it is injured). AL (diallyl-thiosulfinate); AL, the main active ingredient of A. sativum is considered as the most important alkaloid that was generally presumed to be responsible for their useful characteristics (Singh and Sing, 2008).

AL cannot be found in raw garlic, but it is quickly produced by the action of CS-lyase (allinase) on alliin. Allinase is energized by crushing or cutting the garlic cloves (Caporaso et al., 1983; Block, 1985). AL has been reported to have antitumor, antioxidant anti-inflammatory, and antischistosomal effect (Gruhlke et al., 2016; Huang et al., 2017; Metwally et al., 2018).

3.2 The active ingredient of Curcuma longa

Curcumin is a phytochemical present in the Indian spice turmeric, C. longa. As a result of the conjugated system of the molecule, curcumin gives the characteristic yellow color of turmeric. Due to its high coloring strength, curcumin is used in the food and textile industries. It is also used as a preservative (Cohly et al., 2003). Turmeric is composing of curcumin, desmethoxycurcumin, and curcuminoid.

Curcumin is a highly yellow pigment from rhizomatous plant turmeric (C. longa) widely produced in tropical and subtropical areas all over the world, (Černy et al., 2011). Curcumin has limited applications as a drug to treat the disease because of its hydrophobic characteristics and its low oral bioavailability (Prasad et al., 2014; Siviero et al., 2015). Therefore, it is needed to develop a new preparation of curcumin, to enhance the absorption and pharmacological activity In vitro and in vivo researches have reported that curcumin has antitumor, anti-viral, anti-oxidant, and anti-inflammatory properties (Tu et al., 2011; Shi et al., 2017; Wang et al., 2017). C. longa has been approved to have a highly anti-schistosomal effect (Mahmoud and Elbessoumy, 2014).

4. In vitro and in vivo importance

In vitro studies represent essential tools as the worms can be subjected directly to the tested substance without any external influences. In this step, the function is selecting substances that may have some biological effects so it can then be tested whether the effect is repeated in vivo (Simões et al., 2015).

In the last decade, there was a general trend toward testing the efficacy of the different drugs in vitro (Simões et al., 2015; Hassan et al., 2016; Matos-Rocha et al., 2107).

In vivo studies also play an essential tool in the estimation of the quality of the different drugs and to link the tested substances and their side effects within the animal's body. Many previous studies qualify the drugs on S. mansoni in vivo (El-Shenawy et al., 2006; Othman et al., 2009; Ali et al., 2015a; Aboueldahab and Elhussieny, 2016).

5. Parasitological studies

5.1 Mortality rates

The main aim of any drug against schistosomiasis is to achieve high mortality rates in different developmental stages. A. sativum was tested before and found to have a high biocidal effect against miracidia, and cercaria (Mantawy et al., 2012). C. longa plant extract also has potential against cercariae as it resulted in ultrastructure distortions which resulted in a deficient in cercariae capability in infecting mice (Shoheib et al., 2008).

Mohamed et al. (2005) found that Nigella sativa seeds caused in vitro 100% mortality at 100 ppm for S. mansoni males and 110 ppm for female worms. Piper tuberculatum caused 100% mortality in vitro at different concentrations after three days of exposure (Simões et al., 2015). Metwalley (2015) found that A. sativum resulted in the highest in vitro mortality rates of S. mansoni worms in comparison with Dryopteris filixmas, Tanacetum vulgare, Juglans nigra, and Syzygium aromaticum. LC50 of Cerastes cerastes venom caused in the Vitro mortality rate of 83.3% and 50% for male and female S. mansoni, respectively (Hassan et al., 2016).

S. mansoni infected mice which were treated with Acacia senegal showed the highest reduction rate of worms 75.6%, while there was a reduction in the efficacy of PZQ as the reduction rate of worms was 28.7% (Selem et al., 2018). On the other hand, Hussein et al. (2017) recorded that PZQ-treated mice recorded high reduction rates of total worms 90%. In turmeric –treated mice, the reduction rate was 33%. The combination of PZQ+ turmeric resulted in a 100% reduction of total worms (Hussein et al., 2017).

The highest 100% mortality rates were recorded in animals treated orally with 160 mg/kg/day of Clerodendrum umbellatum, while those groups received oral treatment of 80 mg/kg/day or 40 mg/ kg/day of C. umbellatum which caused mortality rates of 88.74% and 73.62%, respectively (Jatsa et al., 2009). In groups treated with Allium sativum either 3 or 7 weeks post-infection, there was a significant reduction ($P < 0.05$) in the worm number and marked mortality rates (Metwalley, 2015). Abououf et al. (2018) found that the in vivo treatment with N. sativa oil had a marked significant effect on the elimination of worms, as the reduction percentage was 57.5%.

5.2 Morphology and ultrastructure changes

In the dorsal side of the adult male worms, there were tubercles with numerous spines randomly distributed throughout the body and the area between the oral and ventral suckers did not have any tubercles, spines, or sensory papillae (Lima et al., 2011; Abdel-Zaher et al., 2016).

The female tegument is smooth without tubercles or spines, the mid-dorsal surface of females showing fine circular ridges interspaced with regular clefts and carrying conspicuous sensory bulbs (Abdel-Zaher et al., 2016).

Tegument of parasitic Platyhelminthes is the main protective sheath that improves the defense and also important in the uptake of nutrients, osmoregulation, and excretion. Hence, the importance of topographical studies can clarify aspects of drug-induced damage (Wendt et al., 2018). S. mansoni normal tegument plays the principal role to link the parasite with the intravascular en¬vironment in the host (El-Shabasy et al., 2015). The comprehensive knowledge of tegumental components would be helpful in the development of new drugs (Kamel and El-Shinnawy, 2015).

Ultrastructure changes using an electron scanning microscope contributed to the understanding of the mechanism of treatment of each therapy (Santiago et al., 2014; Abdel-Zaher et al., 2016; Hassan et al., 2016).

5.3 Oogram & Egg load

Previous studies classified the types of eggs in the oogram pattern according to the maturation stages and/or count the total number of eggs to reflect the level of schistosomiasis progress (Metwalley, 2015; Shams El-Din, 2016; Abououf et al., 2018).
Selem et al. (2018) reported that PZQ caused a significant reduction in the average egg load of 1964.8 ± 909.7 in comparison with infected untreated group 8507.4 ± 915.2. The egg load average was enhanced in the group that received a mixture of PZQ and Acacia senegal (950 ± 498.8). Treatment of S. mansoni infected mice with aqueous garlic extract resulted in a significant diminishing in the percentage of mature eggs compared to the untreated mice (EL-Shenawy et al., 2008).

5.4 Histopathological effects of schistosomiasis

The liver tissue sections of the control untreated mice showed the polyhedral hepatocytes with a centrally positioned nucleus and granular cytoplasm. The hepatocytes coordinated in strands

alternating with the blood sinusoid pa network around the central vein. There were negligible amounts of collagen fibers around some hepatic blood vessels (Ali et al., 2015b).

Egg deposition in the central veins and/or blood sinusoids induces the formation of granuloma. The host's defense mechanism cannot perfectly just eliminate the parasite but the body diminishes the damage by surrounding the parasite with a capsule of inflammatory cells (Rashed et al., 1997). The host immune cells' response to S. mansoni egg resulted in granuloma formation in the infected tissues followed by collagen deposition and finally fibrosis (Ortega et al., 2010). Paradoxically, the granulomas were recorded responsible for severe inflammation, tissue eosinophilia, collagen deposition, and fibrosis (Wilson et al., 2007; Hams et al., 2013).

Liver fibrosis is a major complement of granulomatous schistosomiasis mansoni mostly resulting in portal hypertension in infected humans and mice (Bogers et al., 2000). Schistosomiasis caused deformation of hepatic lobules, degradation of hepatic cords, degeneration of hepatocytes, and vacuolation and necrosis as a result of granuloma formation, hypertrophy, and pigmentation of Kupffer cells. Marked depletion of carbohydrates and increased lipid vacuoles also can be observed. (Mostafa et al., 2011; Mahmoud et al., 2016).

C. longa improved the concentration of glycogen in mice livers when compared with those of untreated animals while, PZQ-treated animals revealed more reduction (El-Banhawey et al., 2007). A. sativum caused diminish granuloma formation and enhancement of histochemical changes observed in untreated- animals (Mahmoud et al., 2016). Abououf et al. (2018) reported that animals treated with PZQ showed a significant reduction in granuloma number and diameter when compared with the control group. Granuloma diameter and number were usually estimated as a tool of treatment qualification by many authors (Shams El-Din, 2016; Abououf et al., 2018).

Schistosomiasis showed deformations in the histological tissues rather than the liver such as intestine, kidney, spleen, and lungs (Soliman and El-Shenawy, 2003; Mostafa et al., 2011; Scheer et al., 2014; Dkhil et al., 2016).

6. Schistosomiasis and body indices

Schistosomiasis causing enlargement of the liver as a result of egg deposition in the hepatic tissue, while in the case of the spleen the enlargement occurs due to passive pressure of blood flow and reticuloendothelial hyperplasia (Hamed, 2011; Wilson et al., 2011). S. mansoni-infected animals suffered from significant growth retardation and hepatosplenomegaly (Jatsa et al., 2018).
The reduction in kidney weight in mice infected with S. mansoni infection was represented as a kidney index. The index in the infected mice was reduced by 43% as compared with the non-infected mice (Diab et al., 2013).

7. Schistosomiasis and complete blood count (CBC)

Schistosomiasis caused changes in different parameters (Da Silva et al., 2005; Sorgho et al., 2017). A marked increase in monocytes, lymphocytes, and neutrophils as well as mild eosinophilia were recorded in schistosomiasis (Da Silva et al., 2005; Mohammed et al., 2006).

S. mansoni caused multiple harmful effects of the blood count on infected non-treated mice as diminishing red blood cells and platelets as well as the rise in white blood cells. Treatment with PZQ enhanced the blood profile of erythrocytes and the platelet (Al-kazzaz, 2018).

Infected mice treated with a mixture of aqueous garlic extract (AGE) and garlic oil extract (GOE) showed a significant increase in Hb average in both infected and non-infected groups (Sadrefozalayi et al., 2018). Mahmoud and ELbessoumy (2014) reported that anemia leucopenia, neutropenia, and eosinophilia were observed in infected groups untreated with enhancement in the groups received diet mixed with C. longa extract (300 g/kg/day) for four weeks.

8. Biochemical parameters
8.1 Lipid profile

Many underestimated plants or it is products were used as ant parasitic drugs and at the same time responsible for the enhancement of lipid

lipid profile, oxidative stress, and other biochemical parameters (El-Shenawy et al., 2006; Mahmoud and Elbessoumy, 2014; Oyinloye, et al., 2015).

The estimation of serum total cholesterol (TC) is one of the essential tools in the diagnosis and classification of lipemia. High blood cholesterol is one of the major risk factors for heart disorders (Burtis and Ashwood, 1999). The concentration of serum high-density lipoprotein-cholesterol (HDL-c) diminished significantly in infected untreated mice (Doenhoff et al., 2002). The factors mediated serum cholesterol-lowering effect were produced from S. mansoni eggs, while the adult worms seemed to have little or no effect (Stanley et al., 2009). Rats received garlic extract at a dose of (100 and 600 mg/ml) showed a significant reduction in TC in comparison with its control group (Obisike et al., 2016).

Garlic extract as a treatment of schistosomiasis mansoni did not induce any marked effect on the cholesterol level compared to the infected untreated animals, while the combination of garlic extract and Nigella sativa oil in infected mice caused a significant decrease in the level of cholesterol (El-Shenawy et al., 2008). Curcumin extracts reduced TC levels in the infected-treated groups after two weeks of the treatment in comparison with the infected untreated group (Mahmoud and Elbessoumy, 2014).

The rise in serum triglycerides (TG) is relatively non-specific. A liver disorder resulting from hepatitis, extrahepatic biliary obstruction, or cirrhosis, diabetes mellitus is associated with the increase in TG levels (Burtis and Ashwood, 1999). Serum TG levels increased in infected Nectomys squamipes in comparison with uninfected animals (Amaral et al., 2016). The investigation of the efficacy of resveratrol which is derived from natural sources as a treatment against schistosomiasis mansoni showed that the drug at a dose of 20 mg/kg once daily for two weeks ameliorated serum TG levels in infected treated animals (Soliman et al., 2017).

Row garlic, oil, and powder extracts have recorded multiple activities such as reduction of TC and TG of blood levels during the rich fat meal intake in human research (Bayan et al., 2014).

Mice infected with S. mansoni and that received a normal diet mixed with curcumin (300 g/kg/day) showed a significant decrease in the levels of TG in comparison with infected untreated animals after two weeks of treatment (Mahmoud and Elbessoumy, 2014).

8.2 Liver enzymes

Alanine aminotransferase (ALT) catalyzes the transport of the amino group of L-alanine and α-ketoglutarate to produce L-glutamate. The highest levels were found mainly in the liver and the kidneys, and smaller quantities in the heart and skeletal muscles (Kim et al., 2008). S. mansoni infected mice treated with PZQ sowed a significant reduction in liver ALT activity (Aziz and Aziz, 2017). There was a significant elevation in ALT levels in control animals compared with mice administered with the extract at a dose of 2000 mg/kg (Kariuki et al., 2017). A. sativum reduced the activity of serum ALT in S. mansoni infected mice in comparison with an infected untreated group (Metwally et al., 2018).

In general, the use of phytosome curcumin reduced significantly the activities of ALT and AST (Tung et al., 2017). Curcumin extract induced a significant reduction in ALT activity in mice infected with S. mansoni when compared with control animals after two weeks of treatment (Mahmoud and Elbessoumy, 2014).

8.3 Uric acid and urea

Uric acid is one of the end products of purine metabolism (Johnson et al., 2011). The cellular injury caused the release of uric acid into the extracellular space that crystallizes to produce monosodium urate (MSU) (Shi et al., 2003). The raised uric acid level may be an indicator of renal insufficiency and also is commonly correlated with gout (Burtis and Ashwood, 1999).

The injury produced by S. mansoni in renal tissues was responsible for the marked significant elevation in blood plasma uric acid (Diab et al., 2013). Serum urea of mice infected with S. mansoni was significantly increased. Garlic extract either separately or in combination with N. sativa oil caused improvement in urea levels (El-Shenawy et al., 2008).

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8.4 Oxidative stress

Reactive oxygen species (ROS) are formed by living organisms as a result of cellular metabolism in normal conditions. At low to moderate concentrations, they function in different cell processes, while at higher concentrations, they produce multiple modifications to cell components, such as lipids, proteins, and DNA (Halliwell and Gutteridge, 1999; Valko et al., 2006).

ROS can be classified into two groups of compounds known as; radicals and non-radicals. The common free radicals are oxygen radical (O··2), hydroxyl (OH·), peroxyl radical (ROO·), nitric oxide (NO·), and nitrogen dioxide (NO·2), while the common nonradicals are hydrogen peroxide (H2O2), hypochlorous acid (HOCl), etc (Kohen and Nyska, 2002).
The odd number of the electron(s) of free radicals makes them unstable, with a short life span, and greatly reactive. Because of their high reactivity, they can attract electrons from other stable compounds to obtain stability (Phaniendra et al., 2015). Thus, the molecules that lose their electrons become unstable and free radical themselves, beginning a chain reaction cycle that finally destroying the living cells.

8.5 Lipid peroxidation

The two most ROS that can affect the lipids are mainly hydroxyl radical (HO•) and hydroperoxyl (HO• 2). Each cell can produce about 50 hydroxyl radicals every second. By the end of the day, each cell would produce about 4 million hydroxyl radicals, which can be neutralized or attack different biological molecules (Lane, 2003). Hydroxyl radicals resulted in cardiovascular disease (Lipinski and Pretorius, 2012) and cancer (Kanno et al.,2012).

The process of lipid peroxidation (LPO) composing of three steps: initiation, propagation, and termination (Yin et al., 2011). LPO with unsaturated lipids produces a wide variety of oxidation products. The principal primary products of LPO are lipid hydroperoxides (LOOH). A secondary product during LPO includes; malondialdehyde (MDA), propanol, hexanal, and 4-hydroxynonenal (4-HNE) (Esterbauer et al., 1991).

The levels of MDA were significantly increased in mice infected with S. mansoni. On the other hand, there was a significant reduction in MDA in PZQ when compared with infected-untreated animals (El-khadragy et al., 2019). There was a significant rise in the hepatic MDA (mmol/mg) levels of infected-untreated animals as compared with the uninfected group. The garlic oil extract reduced the MDA levels of both non-infected and infected mice (Sadrefozalayi et al., 2018). Moreover, mice received a normal diet mixed with curcumin (600 mg/kg/diet) for six weeks showed low levels of MDA in both serum (nmol/mL) and tissues (nmol/g tissue) as compared with an infected-untreated group (Mahmoud and Elbessoumy, 2013).

8.6 Anti-oxidants

There are two types of antioxidants known as the enzymatic and non-enzymatic antioxidants alter the free radical different reactions. Body defense itself against ROS by using enzymatic antioxidant mechanisms. The antioxidant enzymes diminish the levels of lipid hydroperoxide and H2O2, thus, they are essential in preventing LPO and maintaining the structure and function of cell membranes. (Koruk et al., 2004).
Glutathione (GSH) can be considered as the most abundant molecule between the endogenous non-enzymatic antioxidants. GSH is a reduced peptide composing of three-amino acids (glutamine, cysteine, and glycine). This tripeptide can be found intracellularly in either an oxidized (GSSG) or reduced (GSH) form (Townsend et al., 2003).

Glutathione reductase (GRx) is an important antioxidant enzyme, which plays a main role in GSH metabolism, reducing glutathione disulfide (GSSG) to the sulfhydryl form, GSH, by the nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) dependent reaction.

The function of the enzyme is to keep the cellular concentration of reduced GSH higher than its oxidized form, GSSG (Ribeiro et al., 2012). GSH is significantly more beneficial than GSSG under healthy physiological states (Ballatori et al., 2009).

Glutathione-S-transferase (GST) are a group of enzymes or binding proteins found in multiple species and tissues. These enzymes are identified to catalyze the conjugation of GSH with numerous electrophilic molecules which are the first step in mercapturic acid formation before elimination. They also work as binding proteins for a variety of carcinogens that do not serve as substrates (Habig et al., 1974).

Superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) are antioxidant enzymes that do not only play an essential but needful role in the antioxidant defense ability of the different biological systems against the free radical offensive. H2O2, when accumulated, is toxic to body different cells (Ighodaro and Akinloye, 2018). The superoxide radical (O2.-) or singlet oxygen radical (1O2−) generated in tissues through metabolism process or reactions in cells are catalytically transformed into H2O2 and molecular oxygen (O2) by (SOD). H2O2, when accumulated, is toxic to body different cells (Ighodaro and Akinloye, 2018). SODs can be mainly classified into four types: iron SOD (Fe-SOD), manganese SOD (Mn-SOD), copper/zinc SOD (Cu/Zn-SOD), and nickel SOD (Ni-SOD) (Abreu and Cabelli,2010).

In the presence of Fe2+, H2O2 is converted to deleterious OH through a Fenton reaction. This process can be prevented by CAT which breaks down H2O2 into water and molecular oxygen. However, CAT is absent in the mitochondria, hence the reduction of H2O2 to water and lipid peroxides to their corresponding alcohols is carried out by GPx (Ighodaro and Akinloye, 2018). In the presence of GSH, GPx catalyzes the reduction of H2O2 and a wide variety of organic peroxides (R-OOH) to the corresponding stable alcohols (R-OH) (Ursini, 1995).

S. mansoni infected-untreated mice showed a significant reduction of CAT activity and GSH level when compared with normal control mice. The CAT activity was increased in mice treated with PZQ in comparison with infected-untreated mice. On the other hand, there was not a significant difference in the level of GSH in infected mice treated with PZQ in comparison with an infected-untreated group (Jatsa et al., 2018). PZQ induced the activities of SOD and GPx in infected mice (Mantawy et al., 2012). GST activity diminishes in the liver homogenate of S. mansoni-infected untreated mice. However, treatment of the infected mice with PZQ at 45, 60, and 75 days post-infection were found to restore the decreased GST activity to its normal level (Sheweita et al., 2010).

There were improvements in the antioxidants (CAT, SOD, and GPx) activities in mice orally treated with garlic by 14.2%, 69.23%, and 56.91%, respectively. The percentage of CAT only increased in the group received a mixture of PZQ and garlic to be 17.47%, while that of SOD and GPx were 50.41 and 48.21, respectively (Mantawy et al., 2012). Infected mice treated with 125 mg kg-1 of AGE or 125 mg/kg of GOE or a mixture of AGE (62.5 mg/kg) and GOE (62.5 mg/kg) showed a significant increase in the level of GSH as compared with infected-untreated animals (Sadrefozalayi et al., 2018). Also, mice received a normal diet mixed with curcumin (600 mg/kg/diet) for six weeks showed a significant improvement of GSH level and activities of CAT and SOD when compared with infected mice (Mahmoud and Elbessoumy, 2013).

9. Genotoxicity

The molecular applications were more recently also used in the evaluation of the therapies' efficacy (de Oliveira et al., 2018). The marked oxidative stress and decreased antioxidant parameters caused by inducer has been found in almost all types of fibrosis and cirrhosis in both clinical and animal models. The disruption of lipids, proteins, and DNA caused by oxidative stress induces necrosis and hepatocyte death as well as the inflammatory response, resulting in final fibrosis (Heeba and Mahmoud, 2014). Severe hepatotoxicity and histological changes resulted in DNA fragmentation and down-regulation of antioxidant gene expression in the liver (Abdel-Wahhab et al., 2017). Hence it is important to grasp the link

between oxidative stress, antioxidant, histological changes, and DNA damage.

More studies give more interest to the role of parasitic reactive electrophilic compounds, e.g., estrogen-as-like metabolites, on the overture of squamous cell carcinoma (SCC) (Correia da Costa et al., 2014; Vale et al., 2017). Maybe, these metabolites can react with host DNA leading to the formation of DNA-adducts and liberation of ROS, inducing a cascade of events that finally leads to the development of SCC. Some evidence mentions that antioxidants can prevent DNA damage (Pinlaor et al., 2009).

DNA fragmentation caused during apoptosis can be categorized into three types; 1) inter-nucleosomal DNA breakage, 2) cleavage into large 50-300 kb lengths and 3) single-strand cleavage process (Bortner et al., 1995). DNA fragmentation and also cellular nuclear condensation can be described as features of the late apoptosis process (Wadskog et al., 2004).

Garlic ingredients including AL have been reported to have antimutagenic effects as mentioned previously by some authors (Siddique and Afzal, 2005; Belloir et al., 2006; Singh et al., 2006). AL inhibited the growth of cancer cells of both murine and human origin. Besides, AL induced the production of apoptotic bodies, nuclear condensation, and a typical DNA ladder found in cancer cells (Oommen et al., 2004).

CU diminished oxidative and nitrative DNA damage by suppression of oxidant-generating genes and enhancement of antioxidant genes, resulting in inhibition of oxidative and nitrative stress in hamsters infected with Opisthorchis viverrini. Hence, CU may be used as a chemopreventive agent to reduce the severity of this parasite s (Pinlaor et al., 2009). CU at a concentration of 25 μM has been reported to induce laddering chromosomal DNA fragmentation in adult filarial worm Setaria cervi in vitro (Nayak et al., 2011).

Inflammation-induced by S. haematobium infection could increase the number of mutant stem cells, in which iNOS-dependent DNA damage occurs via NF-κB activation, leading further for tumor development (Ma et al., 2011).

Schistosomes are identified can disrupt the genetic constitution of their hosts, or, at least, act as apromutagen (Habib et al., 2006; Madbouly et al., 2007). The genotoxic effect of schistosomes and the DNA alkylation high damage observed in the schistosome-infected liver DNA are hypothesized to be caused by free radicals produced during the inflammatory response triggered by schistosomal eggs (Madbouly et al., 2007). The high DNA fragmentation level quantified in hepatic tissues of infected S. mansoni mice correlated with the inflammatory granulomatous response (Aboueldahab and Elhussieny, 2016).

S. mansoni infection caused significant DNA fragmentation in the liver tissues 7 weeks post-infection (PI), compared to infected-untreated. Combined treatment of PZQ and enaminone derivative of 4-hydroxyquinoline resulted in highly significant diminish in DNA fragmentation reaching a level close to that of control at both 7 and 9 weeks PI while, the group treated with PZQ showed no significant change in DNA fragmentation pattern in comparison with the infected untreated group (Eid et al., 2014). In contrast, Aboueldahab and Elhussieny (2016) reported that PZQ treated group showed a reduced level of DNA damage compared to the control ones.

Garlic exerted has not caused major changes in the genome of schistosomes isolated from infected mice after seven weeks of treatment. However, schistosomal mansoni infection caused genetic alterations in the DNA of mice liver, and garlic was able to ameliorate such deformations to a great extent (Riad et al., 2013). DNA fragmentation detection by gel electrophoresis showed that CU (in vitro) induced DNA fragmentation of adult female and male S. mansoni worms. Moreover, TUNEL staining, a technique that detects DNA fragmentation in situ (a hallmark of apoptosis), showed that TUNEL-positive cells increased in adult female and male S. mansoni worms as compared to the negative control group. Also, the number of TUNEL-positive cells was higher in adult female worms in comparison with adult male worms (De Aguiar et al., 2016).

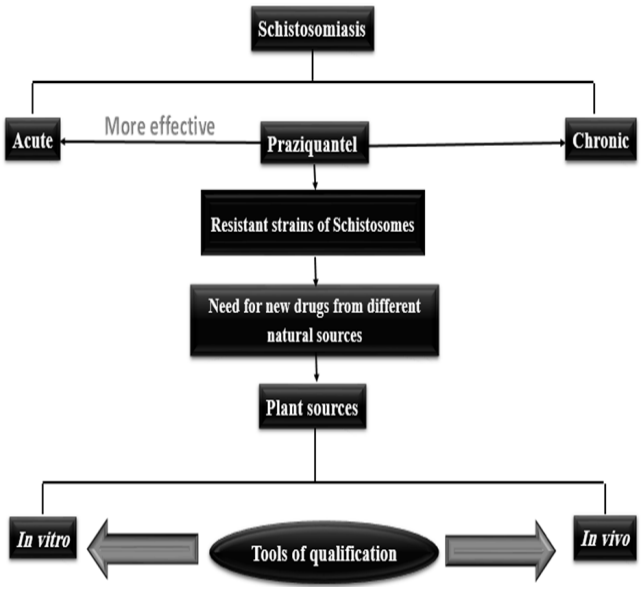

Fig. 1: Diagram summarized the different types of control treatment of schistosomiasis

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