HISTOLOGICAL STUDIES OF THE EFFECTS OF AQUEOUS EXTRACT OF CINNAMON BARK ON THE LIVER OF WISTAR RATS

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SCHOOL OF BASIC MEDICAL SCIENCES
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SUBMITTED TO THE DEPARTMENT OF ANATOMY, SCHOOL OF BASIC MEDICAL SCIENCES, UNIVERSITTY OF BENIN, BENIN CITY, IN PARTIAL FULFILMENT OF THE REQUIREMENT FOR THE AWARD OF BACHELOR OF SCIENCE (BSc.) IN ANATOMY

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CERT IFICATION

I, IKEKU TREASURE ELOGHOSA, hereby certify that the work presented in this thesis for the award of a Bachelor of Science Degree (BSc) in Anatomy is the result of and sole output of an independent research done by me under the Supervision of Dr. Momodu Oghenakhogie and any assistance given has been duly acknowledged. I also certify that this thesis has not been submitted anywhere else in part or in full for any other examination or institution. All literatures and other sources of information consulted, cited or used in this research have been duly acknowledged in references.

DR. MOMODU OGHENAKHOGIE _____

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Date/Sign

DEDICATION

My parents: Rev. and Rev (Mrs) Vincent Ikeku

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ABSTRACT

The application of plants as herbal medicine has been used by various populations throughout human evolution, whereas people started to learn in selecting plants for food, to cure and prevent ailments and diseases. The aim of this study is to investigate the effects of aqueous extract of Cinnamon bark on the liver of wistar rat. Twenty (20) Adult Wistar rats of weighing between 150 g-180g were used for this experiment. The rats were procured from the animal holdings of Department of Anatomy, School of Basic Medical Sciences, University of Benin, Benin City. The animals were housed in the Department of Anatomy, University of Benin. Care and management of animals was carried out in accordance with the guidelines for the care and use of laboratory animals. The animals were allowed to acclimatize for a period of two weeks before commencement of experiment. The bark of Cinnamon was purchased from the vegetable market of "Stop to Shop" located opposite the University of Benin. The bark was chopped into little bits and allowed to dry at room temperature. The dried bark was pounded using wooden mortar and pestle and milled into fine powder in an electric blender. Five hundred grams (500g) of the powder were soaked in 2 liters of distilled water for 24 hours. The mixture was filtered with white filter paper and the residue would be separated from the filtrate. The filtrate was concentrated using Freeze dried technique in the National Centre for Energy and Environment at the University of Benin, Benin City. The rats were randomly assigned into a Control group (A) and three (3) treatment groups (B, C, and D) containing five (5) animals each. Rats in Group B were administered with 200 mg/kg aqueous extract of Cinnamon bark; group C was administered with 500 mg/kg aqueous extract of Cinnamon bark; Group D 1000 mg/kg aqueous extract of Cinnamon bark**.** At the end of the experimental period, the animals were sacrificed using Chloroform anesthesia and the Liver tissues were harvested and fixed in 10% buffer saline for routine histological procedure for hematoxylin and Eosin staining technique. Blood samples were collected from the descending abdominal aorta and preserved, in heparin coated tubes, for biochemical determination of Liver function tests. The data generated carried out using Statistical package for Social Sciences (SPSS) (version 16) manufactured by international Business Machine Corporation (IBM) in Armonk, New York. The significance of the difference in the means of all parameters would be determined using one-way analysis of variance (95% confidence interval). Result obtained showed that the extract had no deleterious effect on the

Liver of the rats. However there was activation of inflammatory cells aggravating toward the portal area. Further studies should be carried out to corroborate this finding.

CHAPTER ONE

INTRODUCTION

1.1 BACKGROUND

The liver is a vital organ in the body is primarily responsible for the metabolism of endogenous and exogenous agents. It plays an important role in drug elimination and detoxification and liver damage may be caused by xenobiotics, alcohol consumption, malnutrition, infection, anaemia and medications (Mroueh *et al.,* 2004). Hepatotoxicity is defined as injury to the liver that is associated with impaired liver function caused by exposure to a drug or another non-infectious agent (Navarro and Senior, 2006). Hepatotoxic agents can react with the basic cellular components and consequently induce almost all types of liver lesions. Toxins and drugs are among the basic etiopathogenetic agents of acute liver failure in Western countries (Grattagliano *et al.,* 2009). Nevertheless, chemical toxins (including acetaminophen, carbon tetrachloride, galactosamine and thioacetamide) are often used as the model substances causing experimental hepatocyte injury in both in vivo and in vitro conditions (Domenicali *et al.,* 2009; Kucera *et al.,* 2006; Ledda-Columbano *et al.,* 1991; Rousar *et al.,* 2009). Despite the fact that hepatic problems are responsible for a significant number of liver transplantations and deaths recorded worldwide, available pharmacotherapeutic options for liver diseases are very limited and there is a great demand for the development of new effective drugs. A number of studies have shown that the plant extracts having antioxidant activity protect against CCl_4 hepatotoxicity by inhibiting lipid peroxidation and enhancing antioxidant enzyme activity (Shahjahan *et al.,* 2004; Sheweita *et al.,* 2001).

Cinnamon (*Cinnamomum zeylanicum* L., Lauraceae) is a tropical evergreen tree and grows wild in Sri Lanka, Madagascar, India and Indochina. The inner bark of the tree has been used in

ethno-medicine and flavoring for foods (Bakkali *et al.,* 2008; Baytop, 1999). In addition to its culinary uses, cinnamon has been employed in traditional herbal medicine to treat a variety of health conditions (Gruenwald *et al.,* 2010). Some studies showed that extracts and its constituents from cinnamon also possess antimicrobial (Carmo *et al.,* 2008; Chao *et al.,* 2000; Dusan et al., 2006; Ranasinghe *et al.,* 2002; Shahverdi *et al.,* 2007), insecticidal (Yang *et al.,* 2005), acaricidal (Fichi *et al.,* 2007), antityrosinase (Marongiu *et al.,* 2007), antioxidant and antimutagenic (Jayaprakasha *et al.,* 2007) activities. In addition, other evidence suggests that cinnamon may be effective in the treatment of cancer (Hyeon *et al.,* 2003; Nishida *et al.,* 2003) and infectious diseases (Hayashi *et al.,* 2007; Premanathan *et al.,* 2000), and that it also shows anti-inflammatory (Hong *et al.,* 2002; Tung *et al.,* 2008), antioxidant (Su *et al.,* 2007; Murcia *et al.,* 2004; Okawa *et al.,* 2001, hypotensive (Preuss *et al.,* 2006), and cholesterol-lowering effects (Khan *et al.,* 2003; Subash Babu *et al.,* 2007).

1.2 STATEMENT OF THE RESEARCH PROBLEM

The application of plants as herbal medicine has been used by various populations throughout human evolution, whereas people started to learn in selecting plants for food, to cure and prevent ailments and diseases. Allopathic medicines are currently used as replacement of traditional medicines, especially in Western developed countries. However, developing countries consume more in traditional medicines due to the increment price of synthetic medicines (Bento *et al.,* 2014; Miraj and Kaini, 2016; Mary *et al.,* 2016). Quinine, digitalis, opium, and aspirin extracted from plants have long history to be used as herbal remedies, and have been developed by various pharmaceutical industries (Padmavathi, 2013). According to World Health Organization, about 80% of residents in Asian and African countries consume herbal medicine as their daily dietary supplements (Gu *et al.,* 2013). Unfortunately, the therapeutic use of natural resources which

mainly consumed by whom cannot afford different treatment has greatly diminished due to the aspects of economic, political and social changes. Several researches are struggling in developing innovative herbal based products with fewer side effects than existing products since medicinal plants chemical composition has become research focus among scientific communities. Plus, the uniqueness of plants' structure, biological and phytochemical properties, has impressed scientists (Bento *et al.,* 2014).

1.3 JUSTIFICATION OF STUDY

Scientists from all places studied biological activity of herbal medicine which based on the different application of different species and scientific use of medicinal plant. Besides, the research also concentrates on how far herbal medicine able to give benefits into pharmaceutical industries. In between 1981 to 2006, there are approximately 50% of drugs derived from natural plant are approved (Gu *et al.,* 2013). Other than that, biological active inside each medicinal plants are established by phytochemical and phytopharmacological sciences where among the biological active constituents are consist of tannins, flavonoids, and terpenoids. These active constituents are highly water soluble, but low absorption due to hardness to cross lipid membrane, huge molecular size, thus resulting into low bioavailability and efficacy (Bento *et al.,* 2014). Therefore, vehicles are needed to be encapsulated with herbal drugs so as to improve drugs solubility, reducing degradation process, minimize toxicity, and level up drugs active absorption resulting into high bioavailability of herbal medicine.

1.4 AIM AND OBJECTIVE OF THE STUDY

The aim of this study is to investigate the effects of aqueous extract of Cinnamon bark on the Liver of wistar rats. The specific objective was to determine the effects of aqueous extract of Cinnamon bark histology of the Liver of the rats .

CHAPTER TWO

LITERATURE REVIEW

2.1 CINNAMON

Cinnamon (*Cinnamomum zeylanicum* L. and *Cinnamon cassia* L.), a species of the *Lauraceae* family, is an evergreen tree of the tropics, which is widely used in medicine, and offers a rich variety of applications worldwide. The word was adopted by English towards the end of 14th century as a loanword from the old French "cinnamone", which in term came from Latin via the Greek-Phoenician word "kinnamomon" and supposed to be from Semitic cf. Hebrew "qinamon". The first appearance of the word in print dates to 1430, in John Lydgate Bochas' "Fall of Princes" (Lankage, 2016).

Cinnamon contains manganese, iron, dietary fibre, and calcium. It has derivatives, such as cinnamaldehyde (CNAD), cinnamic acid, cinnamate, and many other ingredients, such as polyphenols and antioxidants, with anti-inflammatory, antidiabetic, antimicrobial, and anticancer properties. Several reports have shown numerous properties of cinnamon in the form of bark and bark powder. Essential oils and phenolic compounds in cinnamon contribute positively to human health. Studies have recently shown the positive influence of cinnamon in the treatment of Alzheimer's disease, diabetes, arthritis, and arteriosclerosis (Hariri and Ghiasvand, 2016).

Wang *et al* (2013) reported other major compounds in cinnamon: coumarin, cinnamyl alcohol, cinnamaldehyde, cinnamic acid, eugenol, and cinnamyl acetate (Wang *et al*., 2013) Tung *et al* (2010) have also reported the presence of a wide range of essential oils in cinnamon, such as *trans*-cinnamaldehyde, cinnamyl acetate, eugenol, L-borneol, caryophyllene oxide, b-

caryophyllene, L-bornyl acetate, E-nerolidol, α-cubebene, α-terpineol, terpinolene, and α-thujene. Cinnamon consists of a variety of resinous compound. According to other sources, ground cinnamon contains carbohydrates, fibre, moisture, protein, fat, and ash. It also contains vitamins A, B, C, E, K, and lipids. The comsposition is different depending on the geographical origin and the processing methods (Senanayake and Wijesekera, 2010)

As a plant, cinnamon contains many substances and substance groups. Among these, there are essential oils, diterpenes, catechins, proanthocyanidins, tanning agents, colouring agents, phenolic carboxylic acids, lignans, and mucins. Cinnamon's essential oils mainly have antifungal and antibacterial properties and, similarly to cinnamon bark extract, are characterized by antioxidant activity (Perdones *et al.,* 2014). Moreover, essential oils have antiinflammatory, antidiabetic, antitumor, antimutagenic, and memory-enhancing properties. Cinnamaldehyde and eugenol are active components against Gram-positive and Gram-negative bacteria (Sanla-Ead *et al.,* 2021).

Sharifi-Rad *et al* (2021) showed that the bioactive compounds of *Cinnamomum* species possess antimicrobial, antidiabetic, antioxidant, anti-inflammatory, anticancer, and neuroprotective effects. Incomplete knowledge about the safe consumption of higher doses of cinnamon on a daily basis makes it necessary to assess the occurrence of this risk, and therefore, the long-term use of a high amount of cinnamon should be monitored. The tolerable daily intake for coumarin (0.1 mg/1 kg body weight) can be regarded as safe in terms of daily cinnamon intake without the risk of adverse effects (Abraham *et al.,* 2010). According to the scientific data currently available, a risk assessment must be focused on the problematic ingredients of cinnamon extract, especially on coumarin, *trans*-cinnamaldehyde, safrol, and styrene, which are toxic.

Cinnamon bark is obtained twice a year, closely following each of the rainy seasons, when the air humidity facilitates bark harvesting. The first harvest is done when the trees are three years old, a year after pruning. The side stems that are about three-years-old are cut off, and the bark is pulled off. Cinnamon bark is gained only from stems that are between 1.2 and 5 cm in diameter. Cinnamon is often ground to a powder before sale. The powder should be packed in moisture-proof wrapping (polypropylene bags) to keep the flavor. Polyethylene packaging is not advisable, as the flavour components diffuse through it (Azam-Ali, 2007).

Figure 2.1: image of Cinnamon bark (Wang *et al.,* 2021).

2.2 MEDICINAL USE

Cinnamon bark is commonly used as a spice. It is principally used in cooking as a condiment and flavouring agent. It is used in the production of chocolate, especially in Mexico, which is the biggest importer of true cinnamon (*C. zeylanicum* L.). It is also added to desserts, such as apple

pie, donuts, and cinnamon buns, as well as spicy candies, tea, hot cocoa, and liqueurs. True cinnamon and not cassia (*C. cassia* L.) is better for use in sweet dishes (Azam-Ali, 2007). In the Middle East, it is often used in savoury dishes of chicken and lamb. In the USA, cinnamon is often used as an additive to flavour cereals, bread-based dishes, and fruit, especially apples; and a cinnamon–sugar mixture is on sale in grocery stores. Another use of cinnamon is in pickling (Wang *et al.,* 2021).

Cinnamon bark is one of the rare spices that can be consumed directly; cinnamon powder has long been an important spice in Persian cuisine, added to various thick soups, drinks, and sweets. It is often used as a mixture with rosewater or other spices to make a cinnamon-based curry for stews or just sprinkled on sweet desserts (Wang *et al.,* 2021).

2.2.1 EFFECTS IN HUMANS

Cinnamaldehyde (CNAD) lowers inflammatory reactions, oxidative stress, and apoptosis of the liver in *Salmonella typhimurium*-infected mice. Supplementation of CNAD might be a good preventive method to alleviate the liver damage caused by *Salmonella typhimurium* infection in humans and animals (Wang *et al.,* 2021).Moreover, cinnamon bark essential oils (EOs) have been shown to cause oxidative stress to *Klebsiella pneumoniae*, resulting in the loss of cell viability (Yang *et al.,* 2019). Both oregano and cinnamon bark EOs have strong antibacterial properties. Aljaafari *et al.* (2021) have shown that the antimicrobial properties of essential oils (EOs) are based on the mode of action in relation to membrane disruption, efflux inhibition, the increase in membrane permeability, and the decrease in intracellular ATP. These essential oil compounds can be used as potential agents against bacteria, fungi, and viruses. In the future, the integration of EOs uses can lead to many clinical applications.

In medicine, the essential oils in cinnamon behave like other volatile oils. It has also been used in the treatment of digestive system problems and colds. The essential oils in cinnamon also have antimicrobial properties and are used as a preservative in some foods. Cinnamon has been reported to have remarkable pharmacological effects in the treatment of diabetes type 2 resistant to both mellitus and insulin; however, the plant material used in the study was mainly from cassia and only some of the plant material was from *C. zeylanicum*. Cinnamon has traditionally been used for toothache and to fight bad breath, and its regular use is thought to cure the common cold and support digestion **(**Jing *et al.,* 2018**)**. It is noted that regular drinking of *C. zeylanicum* tea made from the bark could be helpful in oxidative-stress-related illness in humans, since it has considerable antioxidant potential. Cinnamon may also act as an aphrodisiac. One teaspoon of cinnamon has as many antioxidants as a cup of pomegranate juice and half a cup of blueberries **(**Jing *et al.,* 2018**)**. Nanocapsules with cinnamon-thyme-ginger composite essential oils prepared with chitosan as the wall via ionic gellification reaction were tested in medicine and revealed durable antibacterial activity against *Escherichia coli*, *Bacillus subtilis*, and *Staphylococcus aureus*. Composite essential oil nanocapsules CEO-NPs can be applied as a strong long-lasting natural preservative **(**Jing *et al.,* 2018**)**.

2.2.2 ADVERSE EFFECTS REPORTED IN HUMANS

Scientific research has confirmed the effectiveness of cinnamon in fighting microbes, viruses, fungi, oxidants, tumours, and hypertension. It also has antidiabetic, gastro-protective, and immune modulatory potential (Grant-Alfieri *et al.,* 2013). However, the popular use of cinnamon has also resulted in several reports of side effects from its short- and long-term use. The most common negative effects were disorders of the stomach and bowels, as well as allergic reactions,

which were self-controlling in most cases. Although cinnamon is safe as a spice and/or flavour, prolonged and enlarged use may be a health risk, and hence, in medicinal uses, it should be clinically monitored (Hajimonfarednejad *et al.,* 2018). Cinnamon coats and dries the mouth and throat, leading to coughing, gagging, vomiting, and the inhalation of cinnamon, causing throat irritation, breathing difficulties, and a risk of pneumonia or lung collapse (Grant-Alfieri *et al.,* 2013). Cinnamon contact stomatitis (CCS) is also a sporadic reaction to the consumption of foods containing artificial cinnamon flavor. Physicians who treat patients with oral conditions ought to be aware of CCS to correctly diagnose and manage this condition (Georgakopoulou, 2010). Contact stomatitis, which is related to the use of cinnamon flavorings, is rather rare. The symptoms, as well as the histopathologic features of this disease are non-specific. They may be similar to other inflammatory illnesses of the oral mucosa, which causes problems in diagnosis. Patients develop white and erythematous spots of rapid occurrence, with an associated sensation of burning. High levels of coumarin and cinnamaldehyde might be associated with mouth sores (Vivas and Migliari, 2015). High levels of coumarin and cinnamaldehyde might be also correlated to liver damage and low blood sugar (Deng, 2012); such high levels may increase the risk of cancer, breathing problems, and interaction with certain medications (Abraham *et al.,* 2010).

Oral lesions caused by a reaction to cinnamon flavouring agents are rather uncommon and are probably unrecognized by many physicians. Most patients feel a “burning sensation”, which is the primary symptom. Clinically, lesions present as erythematous patches with different degrees of superimposed keratosis or ulceration. The lesions are usually limited to the buccal mucosa and lateral border of the tongue. The responsible agent was most frequently cinnamon-flavouring

chewing gum, and symptoms usually eased within 1 to 2 days after the last use of the product containing cinnamon (Allen and Blozis, 1998).

2.2.3 FUNGICIDAL ACTIVITY

Cinnamon oils and extracts possess antifungal properties against serious plant diseases. Wilson *et al.* (1997) indicated that, out of 49 essential oils tested, cinnamon leaf *C. zeylanicum* showed the strongest antifungal activity against *Botrytis cinerea*. Montes-Belmont and Carvajal (1998) found that *Aspergillus flavus* was fully inhibited by *C. zeylanicum*. In other studies, *C. zeylanicum* proved to be fungicidal towards pathogens (*Colletotrichum musae*, *Lasiodiplodia thebromae*, and *Fusarium proliferatum*) isolated from bananas (Ranasinghe *et al.,* 2002) Cinnamon also had an antifungal effect against *Oidium murrayae* (Chu *et al.,* 2006) and harnessed conidial germination of *Colletotrichum gloesporioides* (Barrera-Necha *et al.,* 2008). In in vitro tests, it proved to have a significant mycelial inhibition in corn rot *Fusarium oxysporum* f. sp. *gladioli* (Barrera-Necha *et al.,* 2009) and to be very effective against the growth of *Rhizoctonia solani* (Nguyen *et al.,* 2009). Moreover, cinnamon has powerful antifungal activity towards early tomato blight (*Alternaria solani*) (Yeole *et al.,* 2014). *Botrytis cinerea* is a serious problem, especially in horticultural crops. The investigations of Wang et al. (2014) demonstrated that cinnamon microemulsions possessed high in vivo control properties against gray mould of pears, *B. cinerea.* Cinnamon bark powder and also its water suspensions and filtrates controlled *B. cinerea*; moreover, tomato plants sprayed with cinnamon developed better than the control plants (Kowalska *et al.,* 2020).

An in vitro study on extracts from the cinnamon bark of *C. cassia* and clove (*Syzygium aromaticum* L.) on the growth of *B. cinerea* colonies showed their antifungal activity, causing a

slow growth of this pathogen and can be applied to control strawberry gray mould. The clove extract consisted of 52.88% eugenol, and the cinnamon extract consisted of 74.67% cinnamaldehyde. The efficacy of the extracts on detached strawberry leaves showed that a 12 mL/L concentration of clove extract was effective in suppressing grey mould infection. It is worth noting that the results indicate that the antifungal properties of the clove extract were more effective (even applied in a lower concentration) than that of the cinnamon extract. Grey mould infection on detached strawberry leaves was inhibited by the use of clove oil at the higher investigated concentration (12 mL/L) (Oliveral *et al.,* 2016). The cinnamon extract applied at a rate of 12 mL/L proved to be less effective at inhibiting the spread of grey mould on strawberry leaves (Sernaite *et al.,* 2020), and Allam *et al.* (2017) reported that a higher concentration of 20 mL/L of cinnamon entirely inhibited the mycelial growth of *B. cinerea* in vitro.

Cinnamaldehyde has been used effectively as a bio-fungicide for controlling other plant fungal diseases. For example, it showed good inhibitory activity against *Colletotrichum lagenarium*, a significant plant-pathogenic fungus leading to anthracnose of cucumber. Other studies indicate that it markedly inhibited zoospore germination and the rapid mycelial development of *Phytophthora capsici*, a pathogenic fungus causing phytophthora blight of pepper (Yan-Feng *et al.,* 2015). Essential oil extracted from *C. zeylanicum* (CEO) leaves was identified as having the active constituents eugenol and *trans*-cinnamaldehyde, which had, respectively, minimal inhibitory concentrations (MICs) of 250 and 62.5 µg/mL against *Alternaria alternata*, while, under the same conditions, the MICs for a commercial fungicide and CEO were 1250 and 500 µg/mL, respectively (Pernia *et al.,* 2019).

Cinnamon essential oil proved to be more capable of limiting the incidence and progress of fungal disease in commercial tangerine orchards than copper fungicide and was effective at a

similar level as a commercial plant activator. Both essential oil and cinnamaldehyde (additional to the direct way of action, inhibiting fungal growth), positively influence the plant defense system; causing a significant rise in enzyme levels (Pernia *et al.,* 2019).It was conferred that cinnamon oil has powerful antifungal activity against these four species of fungi: *Aspergillus niger*, *Penicillium notebookum*, *Mucora heimalis,* and *Fusarium oxysporum*. Cinnamon oils and cinnamon extracts have demonstrated good antifungal properties against economically important plant diseases [**41**]. The effectiveness of essential oil from clove and cinnamon against fungi resulting in the postharvest decay of grapes: *A. niger*, *A. alternata*, *Colletotrichum gloeosporioides*, *L. theobromae*, *Phomopsis viticola*, and *Rhizopus stolonifer* has also been investigated. In the study of Udomlak *et al*. (2017), the antifungal activity of clove oil against all the above-mentioned fungi showed minimal inhibitory concentrations (MICs) of: 200, 200, 400, 800, 200, and 200 mg/mL, respectively, whereas the MICs obtained from cinnamon oil were 50, 100, 200, 200, 100, and 800 mg/mL, respectively. Investigation of the synergistic effect of clove and cinnamon oil showed three optimum ratios: 3:7, 2:8, and 1:9 and MICs for all fungi obtained from these ratios for the inhibition of the growth of six fungi was 400 mg/mL. A study of the synergistic effect of clove and cinnamon oil indicated three optimum proportions: 3:7, 2:8, and 1:9, and the MICs for all fungi obtained from these ratios to inhibit the development of six fungi was 400 mg/ mL (Udomlak *et al*. 2017), A further study determined if essential oils can be applied as a contact fungicide seed treatment for organic maize. The sowing date for organic maize (*Zea mays* L.) is delayed to avoid the coldness and wetness of spring soils. Conventional farmers can apply chemical fungicide seed treatments to protect the emerging seedling but almost no organic fungicides are on the market. Eighteen plant essential oils were studied for their fungicidal activities against three common maize

pathogens: *Penicillium* spp., *Fusarium* spp., and *Pythium* spp. Five oils fully controlled all three pathogens in vitro. These oils were cinnamon, clove, oregano, savory, and thyme. The MIC for all pathogens was 800 µL/L, and no phytotoxicity was detected in the germination test at doses up to 16,000 µL/L (MIC × 20). The field emergence of inbred and hybrid seeds treated with the essential oil were considerably decreased compared to seed treated with the commercial, conventional fungicides and one organic fungicide (Christian, 2007).

Fusarium wilt caused by *F. oxysporum* f. sp. *lycopersici* is the most serious disease of the tomato. In the study of Prashant et al. (Yeole *et al.,* 2016) seven plant extracts were screened against *F. oxysporum.* Among these, the antifungal properties of *S. aromaticum* and *C. zeylanicum* extracts were comparable to the efficiency of chemical fungicides. Methanol (MeOH) extract of *S. aromaticum* demonstrated the widest range of inhibition as compared to other extracts assessed, including those from *C. zeylanicum*. Solvent extracts of cinnamon and clove proved to be 100% inhibitory against *F. oxysporum* spores at 5 and 10 mL/L rates (Yeole *et al.,* 2016).

Another pathogen, *Fusarium verticillioides,* is a filamentous fungus and a commonly occurring pathogen with the ability to infect and destruct economically important crops by producing fumonisin mycotoxins. Xing *et al.* (2016) carried out a study to assess the inhibitory properties of cinnamon and clove, eucalyptus, anise, spearmint, and camphor oils on *F. verticillioides*. Cinnamon oil proved to have the strongest inhibition properties. The antifungal potential of cinnamon oil was investigated with a special focus on its mechanism of inhibition of *F. verticillioides* development at the morphological and ultra-structural planes. For *F. verticiliides*, the minimal inhibitory concentrations (MICs) of cinnamon oil (85% cinnamaldehyde), natural cinnamaldehyde (95%), and synthetic cinnamaldehyde (99%) were 60, 50, and 45 mL/L, respectively. The same authors (Xing *et al.,* 2014) used scanning electron microscopy and its

transmission version of *F. verticillioides* in the presence of MIC of cinnamaldehyde and showed irreversible deleterious morphological and ultra-structural changes, such as a lack of cytoplasmic content, depravation of integrity and rigidity of the cell wall, plasma membrane disintegration, mitochondrial destruction, and the folding of the cell. These alterations caused by cinnamaldehyde may result from its interference with the enzymatic reactions of cell wall synthesis, thus negatively influencing the morphogenesis and development of the fungus. These outcomes further emphasized the toxicity of cinnamon oil towards *F. verticillioides* attacking grains. It shows that cinnamon oil can be safely applied as an alternative to chemical fungicides during grain storage. The cinnamon oil concentration proved to be effective on the development of *F. verticillioides* with fumigation. The inhibitory effect of cinnamon oil rose proportionally to its concentration and proportionally to treatment duration. An increase in cinnamon oil concentration resulted in a delay in conidia germination and showed different inhibitory reactions. At a rate of 40 mL per Petri dish after 6 days of incubation, the cinnamon oil fully inhibited *F. verticillioides* mycelial growth. After 20 days of incubation, visible development of *F. verticillioides* did not take place. These results indicate the fungistatic properties of cinnamon oil at lower ratios and fungicidal properties at higher ratios (Xing *et al.,* 2014). The ability of cinnamon, clove, lemongrass, oregano, and palmarosa essential oils to prevent the growth of fumonisin B1 (FB1) production by *F. verticillioides* at different water activities (0.95 and 0.995 aw) and temperatures (20 and 30 °C) in irradiated maize grain was also evaluated by Velluti *et al.* (2004). All of the essential oils inhibited growth of *F. verticillioides* isolates under all conditions tested, but FB1 production was only inhibited at 30 °C and 0.995 aw.

The antifungal properties of cinnamon against other pathogens have been shown by other researchers (Sarkhosh *et al.,* 2018). The in vitro efficacy of cinnamon essential oil was tested at

application rates of 100, 250, 500, 1000, and 2000 µL/L for controlling fruit rot. The mycelium growth of *Colletotrichum gloeosporioides* sp., *Fusarium solani*, and *Phytophthora palmivora* was inhibited at application rates of 1000 µL/L (Sarkhosh *et al.,* 2018). The antifungal effect of cinnamon oil has been studied with special reference to its mechanism of inhibition on *F. verticillioides* growth at the morphological and ultra-structural levels. The MICs of cinnamon oil (85% cinnamaldehyde), natural cinnamaldehyde (95%), and synthetic cinnamaldehyde (99%) were 60, 50, and 45 µL/L, respectively. The antifungal activity of cinnamon oil was proportional to its cinnamaldehyde concentration (Xing *et al.,* 2014). A significant antifungal effect was observed with the essential oil of C. *zeylanicum* on mycelial growth using bioassays of *Fusarium oxysporum* f. sp. *gladioli* at 100, 150, 200, 250, and 300 ppm (Barrera-Necha *et al.,* 2009). The important antifungal potential of cinnamon oil (both in vitro and in vivo) in proportion to its concentration towards various *Fusarium* species was confirmed. In in vitro studies by Horváth *et al.* (2013) the cinnamon oil effectively controlled mycelial development of Fusarium head blight of winter wheat. Jiang *et al.* (2013) demonstrated that *C. cassia* oil has a significant antifungal effect against *S. sclerotiorum* with a minimum inhibitory concentration (MIC) of 256µg/mL in agar and 64µg/mL in air. In a further study, *trans*-cinnamaldehyde exhibited the highest antifungal activity among the three cinnamaldehydes tested. Al-Taisan *et al.* (2014) noted that cinnamon, clove, and mint oils completely inhibited in vivo mycelial growth of *S. sclerotiorum* at 10–500 ppm concentrations. A soil application containing cinnamon oil significantly reduced the incidence of disease caused by *S. sclerotiorum*, producing 75% plant survival compared to the control (Christian, 2007). Moraes *et al.* (2018) investigated the inhibitory properties of cinnamon (*C. cassia*) and citronella (*Cymbopogon winterianus*) essential oils in the in vitro control of *Aspergilus* sp. and *S.*

sclerotiorum fungi. The effectiveness of cinnamon and other essential oils and microelements against *Sclerotinia sclerotiorum* was shown in in vitro tests. Cinnamon and citronella essential oils were used in doses of 0.2, 0.4, 0.8, and 1.6 mL/L. The dose of 1.6 mL/L of both oils fully inhibited the mycelial development of *Aspergillus* sp. and *S. sclerotiorum* fungi.

The continuous spread and evolution in the development of natural plant protective means as alternatives to synthetic fungicides attracts attention today. Combrinck *et al.* (2011) evaluated the antifungal properties of eighteen essential oils and their impact on the growth of five pathogens in vitro (*Lasiodiplodia theobromae*, *Colletotrichum gloeosporioides*, *Alternaria citrii*, *B. cinerea*, and *Penicillium digitatum*) isolated from mango, avocado, citrus, grapes, and cactus pear. Most of the oils were chosen because of their commercial availability and the content of a predominant compound. A visual inspection of the fungal growth was conducted, and the lowest ratio where the fungal growth was fully stopped was noted. Rich in eugenol (81.2%), cinnamon oil showed a strong fungicidal effect [45]. In other research, the antifungal properties of cinnamon extract (CE) were assessed on banana crown rot fungi. The antifungal activities of cinnamon extract, pepper extract (PE), and garlic extract (GE) were evaluated on banana crown rot fungi (*Colletotrichum musae*, *Fusarium* spp., and *L. theobromae*) in vitro. The assay was conducted with extracts of CE, PE, and GE with concentrations of 0, 0.1, 0.5, 1.0, 5.0, 10.0, and 0.75 g/L of carbendazim (CBZ) on potato dextrose agar at room temperature. CE completely inhibited the conidial germination and mycelial growth of all three fungi at 5.0 g/L. PE totally suppressed mycelial growth of all fungi at 5.0 g/L and conidial germination at 10.0 g/L except for Fusarium spp. GE had no significant effects, but low concentrations (0.1 and 0.5 g/L) enhanced germ tube elongation of the three fungi. Crown rot growth was also evaluated during banana storage at 13 °C for 7 weeks. The disease development was weakest (25%) on CE-treated fruit after inoculation and stronger

when CE was applied prior inoculation. CE had no negative effects on the quality of the fruit, but CE used together with hot water treatment led to unacceptable skin browning [53]. The aim of another study was to assess the antifungal potential of crude extracts of cinnamon and rosemary against three isolates of sclerotinia carrot rot both under in vitro and in vivo conditions. The extracts were obtained by applying two different solvents with ethyl acetate (EA) and ethanol. The results indicated that crude extracts of cinnamon can reduce the mycelial development of one isolate at the volatile and contact phase by 35.4% and 78.2%, respectively. Although crude extracts of cinnamon and rosemary could lower the severity of carrot rot during carrot storage in contrast to EA, an extract of cinnamon (2 g/L) was confirmed to have a significant effect against this disease (Ojaghian *et al.,* 2014).

Mohammed *et al*. (2015) studied the potential of *E*-cinnamaldehyde (EC) against *S. sclerotiorum* on potatoes and also the induction of glutathione *S*-transferase genes. The findings indicated that EC could inhibit the mycelial growth of *S. sclerotiorum. E*-cinnamaldehyde decreased white mould on potatoes in greenhouse trials; additionally, *E*-cinnamaldehyde considerably strengthened the activity of glutathione *S*-transferase (GST)-like genes identified from the pathogen genome (Mohammed *et al*., 2015).

Another in vitro study indicated the antifungal activity of five plant extracts, including *C. zeylanicum*, conducted with either cold distilled water (CDW) or boiling water (BDW) on two pathogenic fungi, *A. alternata* and *F. oxysporum.* The results indicate that plant extracts, especially those treated with CDW, revealed a powerful antifungal activity with significant inhibition of the development of the two tested fungi (Fawzi *et al.,* 2009).

2.2.4 BACTERICIDAL ACTIVITY

Imad *et al.,* (2016) established that *C. zeylanicum* possesses remarkable antimicrobial activity, which is predominantly due to *E*-cinnamaldehyde. These findings indicate that the methanolic extract of *C. zeylanicum* is antifungal and antibacterial. Natural biocides with *C. zeylanicum* bark essential oil have major potential as antimicrobials; this potential is reduced due to volatility and the fast decomposition of the essential oil. To prevent this and to lengthen the efficacy of this biocide, cinnamaldehyde (CNAD) was encapsulated into mesoporous silica nanoparticles (MSNPs) in order to handle the problem. To eliminate seedborne diseases, CNAD-MSNPs were dressed in a sodium alginate seed coating. This system was tried against *Pseudomonas syringae* pv. *pisi*, responsible for pea bacterial blight. However, the concentration of CNAD in the alginate coating was <0.0000034% (*v/v*); this was up to 90,000-fold lower than the concentrations of free cinnamon oil reported earlier to control some bacterial diseases Bravo *et al.,* 2018).

2.2.5 INSECTICIDAL ACTIVITY

Cinnamon has been suggested for use as a repellent against insects. Cinnamon oils and their components, such as cinnamaldehyde, are insecticidal compounds that have been used against a variety of insects (Haddi *et al.,* 2017).

Cinnamon leaf oil proved to be very effective as a killing agent for mosquito larvae. The compounds cinnamaldehyde, cinnamyl acetate, eugenol, and anethole, which are ingredients of cinnamon leaf oil, were found to be the most effective against mosquito larvae. The insecticidal and fumigant properties of *C. cassia* bark-derived materials against the oak nut weevil (*Mechoris ursulus*) were examined using filter paper diffusion and fumigation methods. In a test with the filter paper diffusion method, *trans*-cinnamaldehyde showed 100 and 83.3% mortality at rates of

2.5 and 1.0 mg/filter paper, respectively. At 2.5 mg/paper, strong insecticidal activity was produced from eugenol (90.0% mortality) and salicylaldehyde (88.9%), whereas *trans*-cinnamic acid had a moderate activity (73.3%). At 5 mg/paper, weak insecticidal activity (50.0%) was produced from cinnamyl alcohol. In a fumigation study, the cinnamon bark-derived components were considerably more effective in closed cups than in open ones. The results indicated that the insecticidal activity of the tested compounds was attributable to fumigant action, but significant contact toxicity also occurred (Il-Kwon *et al.,* 2000).

Cinnamon oil has been applied to control thrips on onions. The effects of orange and cinnamon oil (from *C. zeylanicum*) on the presence and damage of *Thrips tabaci* on onions was studied. The results (expressed as the number of thrips caught with sweeping nests) confirm that both orange and cinnamon oil considerably reduced the number of adults on onion plants (Pobożniak *et al.,* 2016). To test the controlling potential against agricultural pests, such as the diamondback moth (*Plutella xylostella*), green peach aphid (*Myzus persicae*), and two spotted spider mite (*Tetranychus urticae*), the essential oils of *Coriandrum sativum* and *C. cassia* obtained from steam distillation, hexane extraction, and supercritical extraction were assessed. Using the contact bioassay, the LD_{50} values of *C. cassia* oils prepared by steam distillation and hexane extraction methods were 5.96 and 4.64 μg/cm^2, respectively, against *T. urticae* adults, and the LD_{50} value of the essential oil by the supercritical extraction method was 6.50 μg/cm^2 against *M. persicae* adults. Finally, the research indicated that *C. cassia* oils are a promising natural acaricide and insecticide against pests (Bueyong *et al.,* 2017). In other studies the toxicity and deterrence of the terpenoid constituents of cinnamon oil have been evaluated. The toxic effects, repellent properties, and respiration rate influenced by terpenoid components of cinnamon essential oil were assessed, as well their influence on *Sitophilus granarius* L. The lethal

concentrations (LC_{50} and LC_{90}), repellence in general, and behaviour repellence reaction of adult *S. granarius* in the presence of six concentrations of respective essential oils, as well as terpenoids, were assessed. The chemical constituents of the cinnamon oil were established, and its primary compounds were eugenol (10.5%), *trans*-3-caren-2-ol (10.2%), benzyl benzoate (9.99%), caryophyllene (9.34%), eugenyl acetate (7.71%), α-phellandrene (7.41%), and α-pinene (7.14%). The toxicity of cinnamon essential oil against *S. granaries* was showed. Among the toxic terpenoid components, eugenol has the most powerful contact toxicity against *S. granarius* in comparison to, in decreasing order, caryophyllene oxide, α-pinene, α-humulene, and α-phellandrene. Cinnamon essential oils, as well as their terpenoid compounds, proved toxic and had repellent properties against adult *S. granarius* and thus have preventive and retarding properties for the development of resistance to insecticide (Plata-Rueda *et al.,* 2018).

In another study with storage pests, the bean weevil *Acanthoscelides obtectus*, which is the cause of heavy post-harvest losses in the common bean, *Phaseolus vulgaris*, the essential oil of *C. zeylanicum* was tested for insecticidal (lethal toxicity, disturbances to reproduction, and persistence of action) and repellent activities. The study revealed toxicity at LD_{50} 46.8 µL/kg beans, steadily reduced the growth rate of *A. obtectus* in a dose-related manner, and showed a similar loss of its insecticidal potential with time. Cinnamon oil also repelled the bean weevil. The results showed that cinnamon essential oil is an effective tool for protecting stored beans against *A. obtectus* in small storage facilities. Cinnamon oil inhibited the reproduction ability of the flour beetle (*Tribolium castaneum*), the maize weevil (*Sitophilus zeamais*), and the lesser grain borer (*Rhyzopertha dominica*) at a rate of 0.1–0.2%, mixed with wheat or wheat flour (Jumbo *et al.,* 2014).

The insecticidal properties towards adults of *S. oryzae* L. and *Callosobruchus chinensis* were tested by Soon-Il Kim *et al.* (2003). In a test with a filter paper diffusion method at 3.5 mg/cm^2, an extract from *C. cassia* bark and oil was used. An extract from *C. sieboldii* root bark gave 100% mortality at two days after treatment. At 0.7 mg/cm^2, extracts from *C. cassia, C. sieboldii,* and cinnamon oil were highly effective against both species. In a fumigation test with *S. oryzae* adults, the oils were much more effective in closed containers than in open ones, indicating that the insecticidal activity of the oils was attributable to fumigant action. The authors concluded that these plant extracts and essential oils could be helpful in controlling field populations of *S. oryzae* and *C. chinensis*. In another paper on *Cydalima perspectalis,* the results point to cinnamon oil as a good deterrent with the strongest oviposition-deterring effect (Szelényi, *et al.,* 2020).

2.2.6 NEMATICIDAL ACTIVITY

The nematicidal activity of *C. cassia* and *C. zeylanicum* oils (bark and green leaf) and their chemical compounds against adult *Bursaphelenchus xylophilus* was tested by a direct contact bioassay. The LC_{50} values for cassia oils (0.084–0.085 mg/mL) and for cinnamon oils (0.064–0.113 mg/mL) were toxic towards adult *B. xylophilus*. Of 45 tested compounds, *trans*-cinnamaldehyde (0.061 mg/mL) was the most active nematicide, followed by ethyl cinnamate, α-methyl-*trans*-cinnamaldehyde, methyl cinnamate, and allyl cinnamate (0.114–0.195 mg/mL). Potent nematicidal activity was also observed with 4-methoxycinnamonitrile, *trans*-4-methoxycinnamaldehyde, *trans*-2-methoxy-cinnamaldehyde, ethyl α-cyanocinnamate, cinnamonitrile, and cinnamyl bromide (0.224–0.502 mg/mL). The tested compounds have been

described as potential nematicides to combat *B. xylophilus*, which causes pine wilt disease (Kong *et al,* 2007).

2.2.7 EFFECT OF CINNAMON OIL ON PLANT GROWTH

The impact of seed dressing with various concentrations of cinnamon oil and tea tree oil on the field emergence and yield of parsley var. Berlinska and lettuce var. Ewelina is presented in the literature [67]. Cinnamon oil lowered the lettuce and parsley field emergence. The toxicity was the greatest at 15% concentration. Tee tree oil showed no toxicity in 55 and 70% concentrations and increased the field emergence ability, particularly in lettuce. A similar relation was established for the speed and spread of emergence. A 15% concentration of cinnamon oil caused a decrease in the number of plants for both species (Orzeszko-Rywka *et al.,* 2012).

In laboratory and greenhouse investigations, the allelopathic effect of essential oils extracted from aromatic plants (cinnamon, lavender, and peppermint) on the seed germination of mediterranean weed species (*Amaranthus retroflexus* L., *Solanum nigrum* L., *Portulaca oleracea* L., *Chenopodium album* L., *Sinapis arvensis* L., *Lolium* spp., and *Vicia sativa* L.) was examined. Each essential oil was examined at four concentrations in controlled conditions (germination chamber: 0.2, 0.6, 1.8, and 5.4 mg/L) and in a semi-controlled condition (green house: 5.4, 21.6, 86.4, and 345.6 mg/L). In the controlled conditions, the 1.8 and 5.4 mg/L concentrations stopped seed germination. In the greenhouse (semi-controlled conditions), the 345.6 mg/L concentration of cinnamon essential oil stopped the seed germination of *Amaranthus retroflexus* L. The concentration of essentials oils had a greater effect on weed susceptibility than the type of oil used. However, cinnamon oil had drastic inhibitory effects on germination.

The possible use of essential oils as natural herbicides to control different weeds for the sustainable cropping system has been discussed in relation to their low persistence (due to biodegradability and easy catabolism in the environment); they have no toxicity towards vertebrates, fishes, birds, and mammals and are of importance in plant protection (Cavalieri and Caporali, 2010).

2.3 ORGAN OF STUDY: LIVER

The liver is a vital internal organ and gland in vertebrates and some other animals. It lies majorly in the right hypochondrium and it is separated from the heart and other thoracic viscera by the diaphragm. It is completely surrounded by a peritoneal membrane, known as Glisson's capsule. The organ has a double blood supply; the portal vein and the hepatic artery. Within the liver, the blood passes through the network of micro-vessels, called sinusoids, after which it is collected in hepatic central veins and finally drained by the inferior vena cava. The liver plays a central role in the metabolism of carbohydrates, protein and fats, among other substances, and is thereby important for the maintenance of homeostasis in the body. The liver synthesizes most of the plasma proteins, such as albiumin and globulins. Another function of the liver is detoxification, namely the biotransformation of xenobiotics

compounds, pollutants and drugs into water-soluble compounds which then can be excreted either in bile or in urine. Importantly, the liver also eliminates particulate substances such as bacteria and viruses and different kinds of macromolecules from the blood stream.

2.3.1 ANATOMY OF THE LIVER

The liver is a reddish-brown organ and it is both the largest internal organ and the largest gland in the human body. It has four lobes of unequal size and shape. The human liver weighs about 1500g and weighs about 2%of total body mass of adult (Contran et al., 2005). Anatomically,

based only on external features, the liver is described as having four lobes: right, left, caudate, and quadrate lobe. However, functionally, in terms of blood supply and glandular secretion, the liver is divided into independent right and left lobes. The anatomical large right lobe is separated from the smaller left lobe by the falciform ligament and the left sagittal fissure. The liver is majorly under cover of the rib cage and lies to the right of the stomach and overlies the gall bladder. It is connected totwo large blood vessels; the hepatic artery and the portal vein. Most of the total blood influx is provided by the portal vein bringing nutrient-rich blood from the digestive tract while the hepatic artery delivers blood supplemented with oxygen. These blood vessels subdivided into capillaries which then lead to a lobule. Each lobule is made up of millions of hepatic cells which are the basic metabolic cells. It has two surfaces; diaphragmatic and visceral. The diaphragmatic surface is boldly convex, moulded to the under surface of the

2.3.2 DEVELOPMENT OF THE LIVER

The hepatic diverticulum is seen at the 18th day of gestation (2.5mm stage) as a thickening of the ventral floor of the distal foregut endoderm. This small hepatic diverticulum is the analog for the development of the liver, extrahepatic biliary ducts, gallbladder, and ventral pancreas. Dynamic signaling plays a role for the specification (second stage) of embryonic liver progenitors. Bone morphogcnetic protein from septum transversum, transforming growth factor-beta (TGF beta), and fibroblast growth factor signaling pathways from hepato-cardiac mesoderm converge on the earliest genes that elicit pancreas and liver induction in mouse embryos. The above signaling factors specify the ventral foregut entoderm to become a precursor of hepatic epithelium by expressing several liver-specific genes. The hepatic diverticulum then divides into a solid cranial portion and a hollow caudal one, the cystic part. The cranial part forms the hepatic parenchyma, and differentiates into proliferating cords of hepatocytes and intrahepatic bile ducts, while the

smaller cystic portion is the primordium of the gall bladder, common bile duct and cystic duct. The parenchymal cords anastomose around pre-existing endothelial-lined spaces. They increase in mass and become more organized (Morphogenesis stage) at the expense of the septum transversum that eventually forms the liver capsule. Primitive hepatocytes in contact with the mesenchyme surrounding developing hepatic portal veins form a single structure known as the ductal plate. The ductal plate becomes bilayered with parenchymal and a mesenchymal facing sheet, respectively. The ductal plate consisis of cuboidal cells with increased immunoreactivity for epithelial intermediate filaments such as cyto-keratins relative to the surrounding parenchymal cells. The ductal plate gives rise to cholangiocytes lining the intrahepatic bile ducts, including its most proximal segment. It also generates periportal hepatocytes and adult hepatic progenitor cells. The budding liver invades the viteline veins and then the umbilical veins. Vitelline veins run from gut-yolk sac to the heart. The cranial ends of the veins persist as the portal vein and the cadual ends as the hepatic veins. The hepatocytes grow as thick epithelial plates intermingling branches of vitelline veins within the septum transversum to form a system of connecting liver cells plates. On the other hand, the angioblast forms the liver sinusoids. These sinusoids present by the 5th week of gestation act as templates for the three-dimensional growth of hepatic cords. Initially, liver cell plates are 3 to 5 cell thick. Then gradually they become one cell thick plates. Intrahepatic bile ducts begin to form at 6th week of gestation at the hilum of the liver and gradually reach the periphery at 3 months. By the 5th week, all elements of the biliary tree are recognizable. Marked elongation of' the common duct occurs with plugging of the lumen by epithelial cells. Recanalization of the lumen of the common duct starts at the end of the 5th week and moves slowly distally. By the 6th week, the common duct and ventral pancreatic bud rotate 180 degrees clockwise around the duodenum. Early in the 7th week, the bile and

pancreatic ducts end in closed cavities of the duodenum. Notch signaling is required for normal duct formation. That means it stimulates the cells adjacent to the hepatocyte to differentiate another cell type (duct cells). Notch signals are required for bile duct morphogenesis and activation of Notch signaling in the hepatic lobule promotes on and tubule formation in a dose-dependent manner. The originally hollow cystic portion becomes obliterated owing to the rapid proliferation of its epithelium. At first the gall bladder and common bile duct are solid cords under the developing liver in the 6 to 7mm embryo. Recanalization of the hepatic, common bile duct, cystic duct, and proximal gall bladder then occur by the 16mm embryo. At the third month, the gall bladder is fully open, and connected with the intrahepatic biliary system.

2.3.3 MOLECULAR REGULATION OF THE LIVER INDUCTION

The foregut endoderm has the potential to express liver-specific genes and to differentiate into liver tissue. However, this expression is blocked by factors produced surrounding tissues, including ectoderm noncardiac mesoderm and particularly e notochord The action of these inhibitors is blocked in the prospective hepatic region by fibroblastgrowth factors (FGF2)secreted by cardiac mesoderm and by blood vessel-forming endothelial cells adjacent to the gut tube at the site of liver bud outgrowth Thus, the cardiac mesoderm together with neighbouring vascular endothelial cells “instructs” gut endoderm to express liver-specific genes by inhibiting an inhibitory factor of these same genes. Once this “instruction” is received, cells in the liver field differentiate into hepatoces and biliary cell lineages, a process that is at least partially regulated by hepatocyte nuclear transcription factors (HNF3 and 4) (Sadler.,2012).

2.3.4 ABNORMALITIES

Liver abnormalities are conditions that affect the functions or structure of the liver Abnormalities of the liver could be morphological, vascular, and hereditary.

2.3.4.1 MORPFIOLOGICAL ANOMALIES

Morphological developmental anomalies include: agenesis (absence of a lobe that is replaced by fibrous tissue); aplasia (small lobe with abnormal structure, few hepatic trabeculae, numerous bile ducts, and abnormal blood vessels); and hypoplasia (small lobe but with normal structure). Agenesis of the right lobe of the liver is a rare finding with preservation of the middle hepatic vein. It is usually an incident finding revealed by imaging exams or during abdominal surgery. Hvpoplasia of right hepatic lobe is a rare congenital anomaly that is sometimes associated with ectopy of gall bladder.

2.3.4.2 VASCULAR ANOMALIES

Variation in hepatic arterial anatomy is seen in 40-45% of people. Classic branching of the common hepatic artery from the celiac artery, and the proper hepatic artery into right and left hepatic arteries to supply the entire liver, is seen in 5 5-60%. In general, the common hepatic artery may arise from the abdominal aorta or superior mesenteric artery (SMA), and all or part of the right and left hepatic arteries may arise from other vessels. The two commonest variants are right hepatic artery replaced to the SMA and left hepatic artery replaced to the left gastric artery.

2.3.4.3 HEREDITARY ANOMALIES

Hereditary hemorrhagic telangiectasia (T, Osier-Weber-Rendu syndrorme), is an autosomal dominant vascular disorder with a variety of clinical manifestations (epistaxis, gastrointestinal bleeding, characteristic mucocutaneous telangiectasia). In addition, arteriovenous malformations (AVMs) commonly occur in the pulmonary, hepatic, and cerebral circulations. Large AVMs between the hepatic artery and hepatic vein can cause a significant left-to-right shunt with increased cardiac output (Tsao *et al.,* 2000). Portal hypertension and hepatic encephalopathy,

particularly after episodes of gastrointestinal bleeding, may result both from shunts between the hepatic artery and portal vein, and from increased sinusoidal blood how, leading to enhanced deposition of fibrous tissue and cirrhosis of the liver.

Ataxia-telangiectasia is an autosomal recessive, multisystem disorder characterized by progressive neurologic impairment, variable immunodeficiency with susceptibility to sinusitis and pulmonary infections, impaired organ maturation, x-ray hypersensitivity, ocular and cutaneous telangiectasia, and a predisposition to malignancy. Veno-occlusive disease of the liver may accompany ataxia telangiectasia. Hippel-Lundau disease is a rare autosomal dominant familial tumor syndrome associated with brain, retinal, and spinal cord hemangioblastoma; renal cysts and renal cell carcinoma; pheochromocytoma; and pancreatic cysts, pancreatic serous cystadenomas, and pancreatic neuroendocrine tumors. Liver cysts have been associated with von Hippel-Lindau disease.

2.3.5 DISEASES OF THE LIVER

The liver is a vital organ in the body that supports nearly every other organ in the body in some facet. Without a healthy liver a person cannot 9inive. Common liver diseases include hepatitis A, B, C, D, E, fatty liver disease, cancer, cirrhosis damage from alcohol, the pain reliever acetaminophen, and other cancer drugs. Most times, liver diseases are accompanied by jaundice which is as a result of increased level of bilirubin in the system. The bilirubin accumulates as a result of the breaking down of' haemoglobin which is gotten from the haemolysis of red blood cells. It is the function of the liver to remove bilirubin from the blood and excrete it through bile, but in diseased condition, this function is impaired. Liver diseases may be diagnosed by a liver function test. One advantage of the liver is its ability to regenerate.

CHAPTER THREE

MATERIALS AND METHOD

3.1 ANIMAL CARE AND MANAGEMENT

Twenty (20) Adult Wistar rats of weighing between 150 g-180g were used for this experiment. The rats were procured from the animal holdings of Department of Anatomy, School of Basic Medical Sciences, University of Benin, Benin City. The animals were housed in the Department of Anatomy, University of Benin. Care and management of animals was carried out in accordance with the guidelines for the care and use of laboratory animals (NRC, 1996). The animals were allowed to acclimatize for a period of two weeks before commencement of experiment.

3.2 COLLECTION OF PLANT AND EXTRACTION

The bark of Cinnamon was purchased from the vegetable market of "Stop to Shop" located opposite the University of Benin. The bark was chopped into little bits and allowed to dry at room temperature. The dried bark was pounded using wooden mortar and pestle and milled into fine powder in an electric blender. Five hundred grammes (500g) of the powder were soaked in 2 liters of distilled water for 24 hours. The mixture was filtered with white filter paper and the residue would be separated from the filtrate. The filtrate was concentrated using Freeze dried technique in the National Centre for Energy and Environment at the University of Benin, Benin City.

3.3 EXPERIMENTAL DESIGN

The rats were randomly assigned into a Control group (A) and three treatment groups (B, C, and D) containing five (5) animals each. Rats in Group B were administered with 200 mg/kg aqueous

extract of Cinnamon bark; group C was administered with 500 mg/kg aqueous extract of Cinnamon bark; Group D 1000 mg/kg aqueous extract of Cinnamon bark

3.4 ANIMAL SACRIFICE

At the end of the experimental period, the animals were sacrificed by under chloroform anaesthesia.

3.5 TISSUE PROCESSING

The tissues were trimmed to about 3-5mm thick sections and processed according to method of Drury and Wallington (1980). They were dehydrated for one hour each at room temperature through ascending grades of ethanol: 70% ethanol, 90% ethanol, Absolute ethanol 1 and Absolute ethanol 11. The dehydrated tissues were cleared at room temperature in two changes of Xylene for one hour in each change. The tissues were infiltrated in two changes of molten paraffin wax multi block plastic embedding mould. The paraffin blocked tissues were trimmed and mounted on wooden chunk for sectioning on a rotary microtome. Sections of 5 micrometers thickness were produced from the tissue blocks using a rotary microtome (Bright B5143, Huntington, England). The sections were transferred into water bath at (40°C) to allow spreading of the folded ribbons of sections. These sections were then mounted on new clean glass slide and they were dried at 40ºC on a slide drier to enhance adherence of the sections of the slides. Staining procedures of Hematoxylin and Eosin as described by Drury and Wallington (1980) was adopted.

3.6 HEMATOXYLIN AND EOSIN STAINING

Paraffin wax is poorly permeable to stain, so section was deparaffinized in two changes of xylene for two minutes in each change. Xylene was removed because it does not mix freely with

aqueous solution and low grades of alcohol used in preparing stains. Thus, sections were then hydrated using a series of descending grades of alcohol until water is used. The purpose of this process is to prepare the tissue to stain with a dye that has been dissolved in an aqueous solvent. Procedures of H&E as described by Drury and Wallington (1980) and Scheehan and Hrapchak (1980) were adopted as follows:

a. Sections were dewaxed in two changes of xylene for two minutes in each change;
b. Sections were rehydrated in descending grades of alcohol (absolute I, absolute II, 95%, 90%, 70%, and 50% ethanol) for two minutes each;
c. Sections were rinsed in distilled water for three minutes;
d. Sections were stained in hematoxylin for 15 – 20 minutes;
e. Excess hematoxylin stain were removed by rinsing well in running tap water for two to three minutes (sections would be examined microscopically at this stage to confirm sufficient degree of staining);
f. Sections were differentiated in acid alcohol (0.5% HCL in 70% ethanol) for two to three seconds. The blue staining of hematoxylin changed to red by the action of the acid;
g. Sections were rinsed well in running tap water for 10 – 15 minutes to remove excess differentiator and regain the blue color of the sections as observed with the naked eye;
h. Sections were counter stained in 1% aqueous eosin for two to four minutes;
i. Excess stain were washed off in running tap water and examined under microscope;

j. Sections were dehydrated rapidly in ascending grades of ethanol (50% through absolute ethanol), cleared in xylene and mounted in a synthetic resin medium (DPX) using clean glass cover slip.

3.7 PHOTOMICROGRAPHY

Histological sections were examined under Leica DM750 research microscope with a digital camera (Leica ICC50) attached. Photomicrographs of the tissue sections were taken at various magnifications i.e. x40 and x100.

CHAPTER FOUR

RESULT

4.1: HISTOLOGY:

The result obtained from the histology slides show that aqueous extract of Cinnamon caused severe infiltration of inflammatory cells without any deleterious effect on the hepatocyte and other liver components.

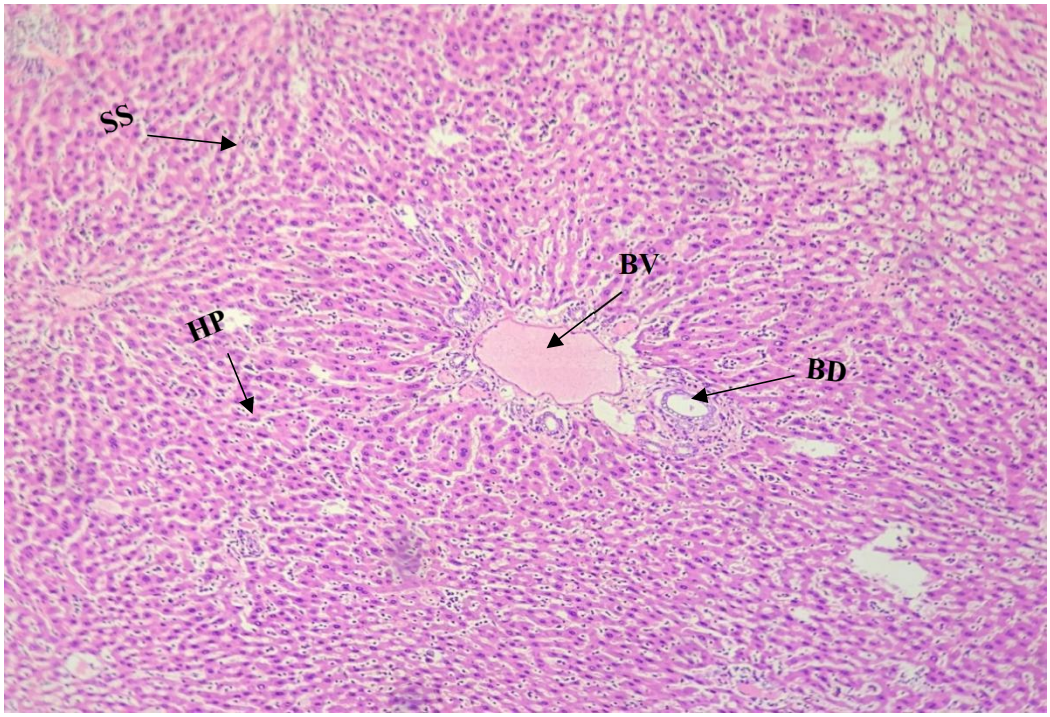

Plate 4.1: Micrograph of liver of rats in the control group (A): HC-Hepatocyte; SS- sinusoid; BV-blood vessel; H&E x 100

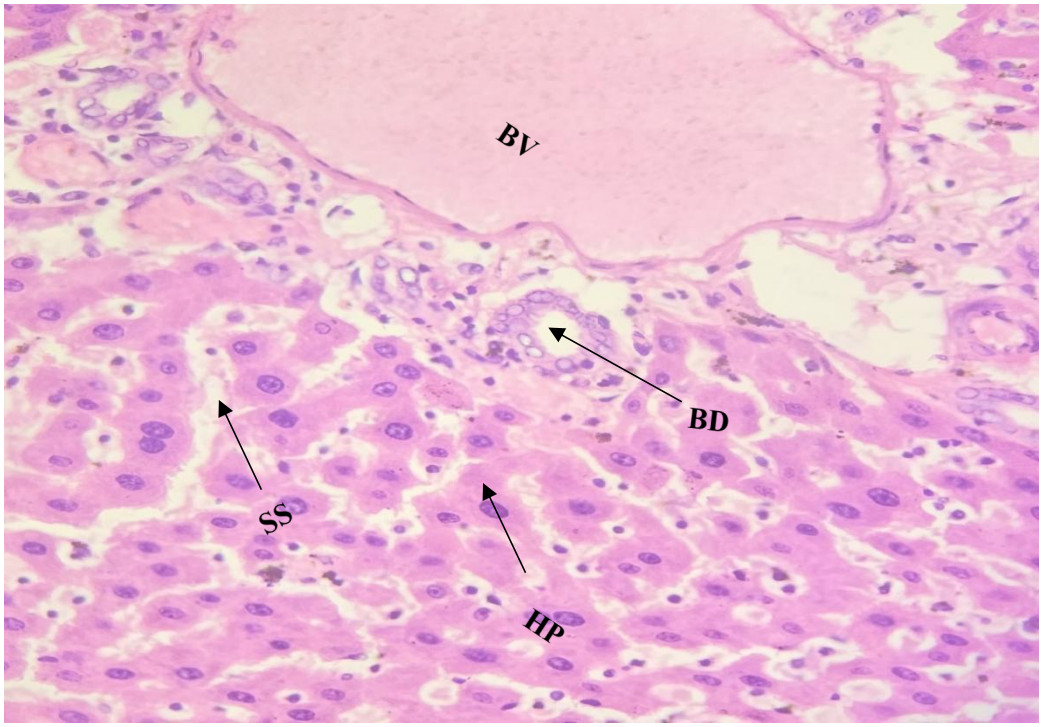

Plate 4.2: Micrograph of liver of rats in the control group (A): HC-Hepatocyte; SS- sinusoid; BV-blood vessel; H&E x 400

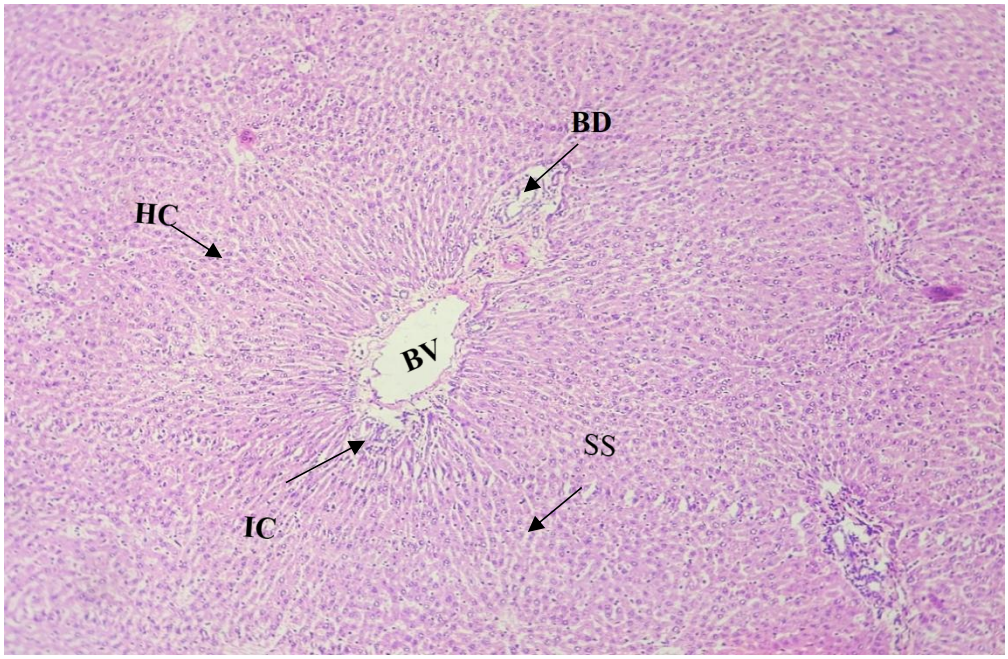

Plate 4.3: Micrograph of liver of rats treated with 200 mg/kg body weight of cinnamon extract (group B): HC-Hepatocyte; SS- sinusoid; BV-blood vessel; IC – Inflammatory cells; BD – Bile duct; H&E x 100

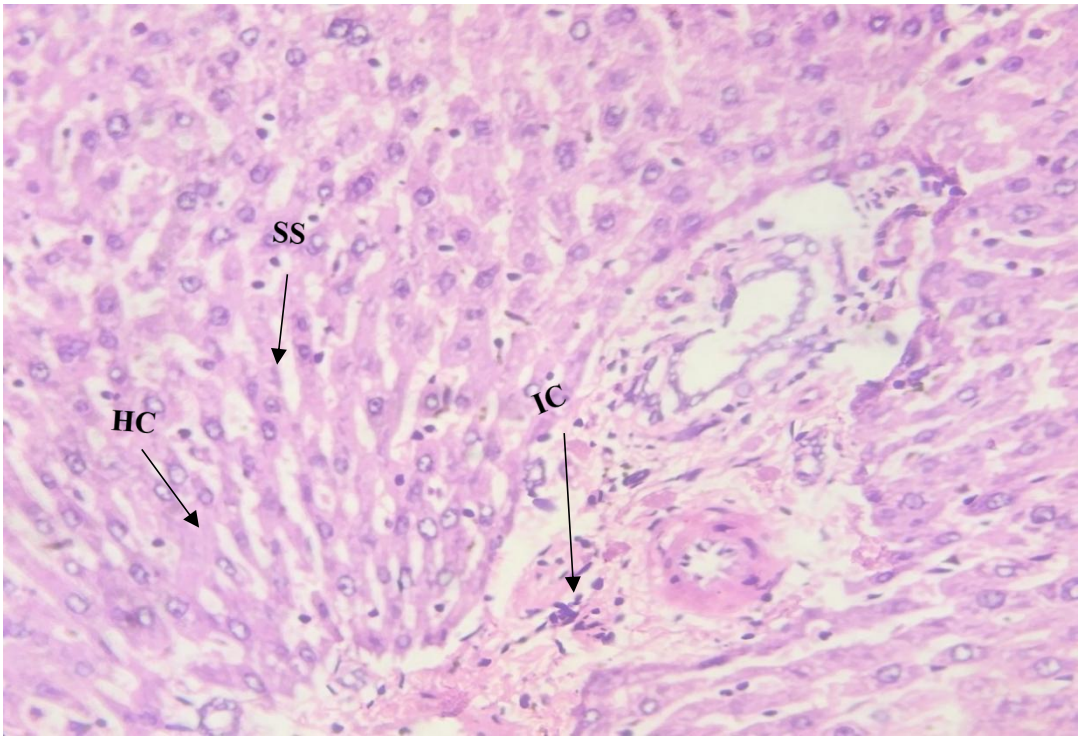

Plate 4.4: Micrograph of liver of rats treated with 200 mg/kg body weight of cinnamon extract (group B): HC-Hepatocyte; SS- sinusoid; BV-blood vessel; IC - inflammatory cells; H&E x 100

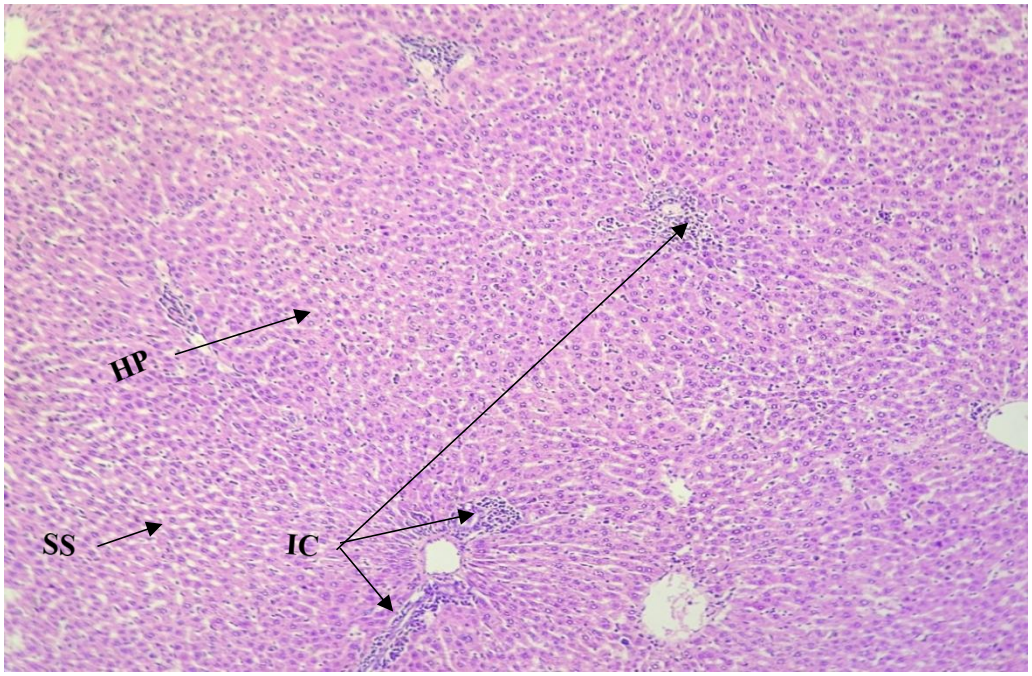

Plate 4.5: Micrograph of liver of rats treated with 500 mg/kg body weight of cinnamon extract (group C): HC-Hepatocyte; SS- sinusoid; BV-blood vessel; inflammatory cells; H&E x 100

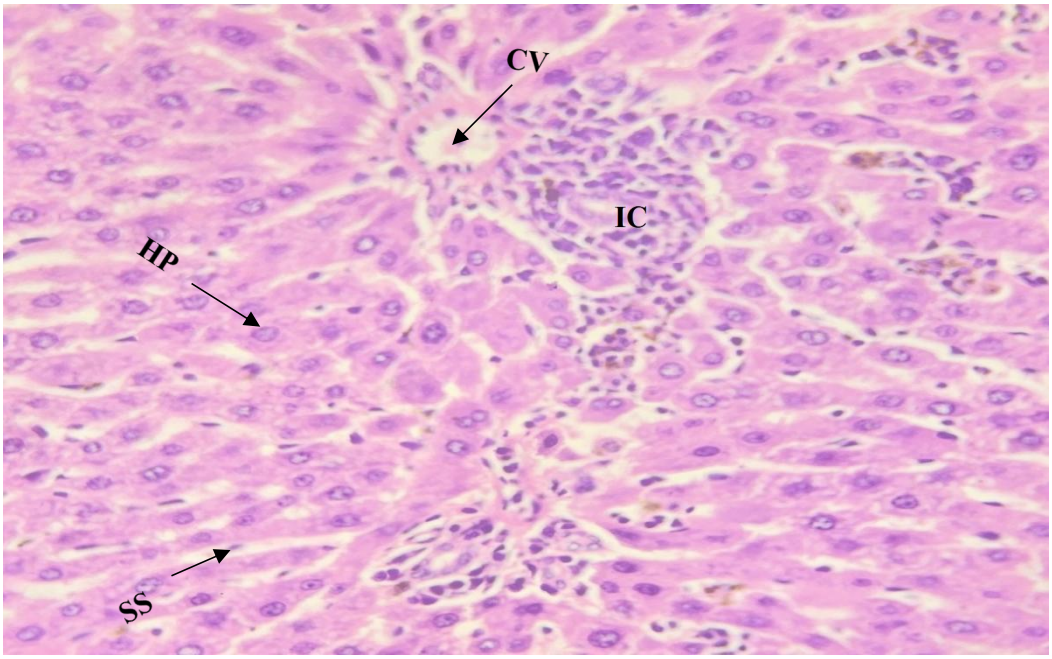

Plate 4.6: Micrograph of liver of rats treated with 500 mg/kg body weight of cinnamon extract (group C): IC – Inflammatory cells; HC-Hepatocyte; SS- sinusoid; BV-blood vessel; H&E x 400

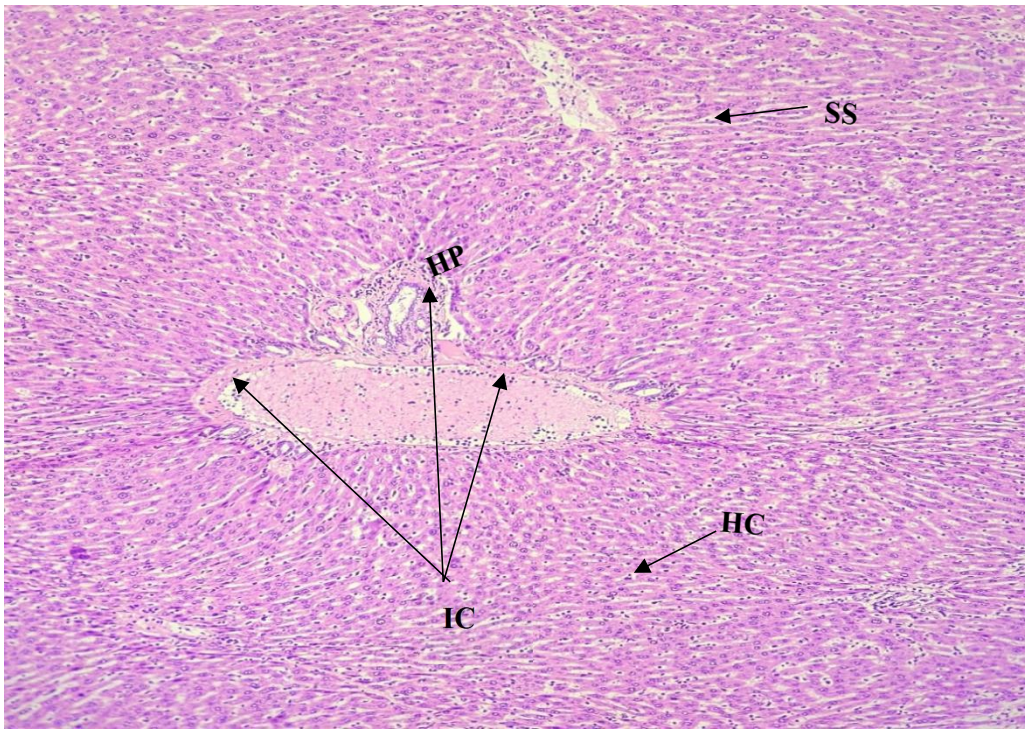

Plate 4.7: Micrograph of liver of rats treated with 1000 mg/kg body weight of cinnamon extract (group D): HC-Hepatocyte; SS- sinusoid; BV-blood vessel; IC – Periportal infiltrates of inflammatory cells; H&E x 100

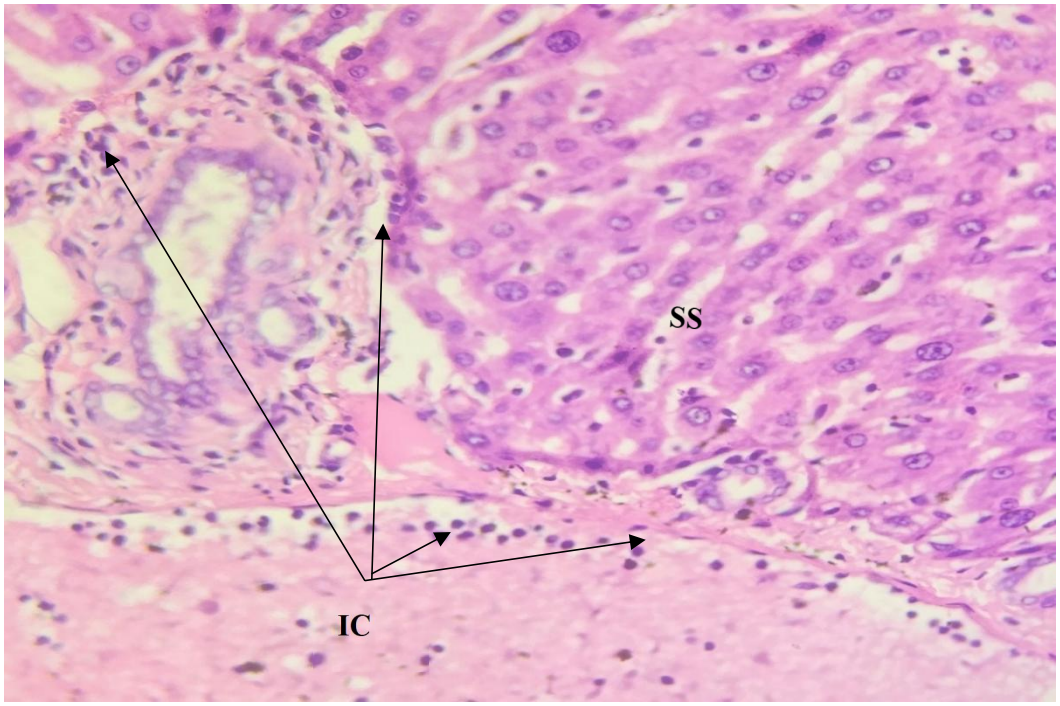

Plate 4.8: Micrograph of liver of rats treated with 1000 mg/kg body weight of cinnamon extract (group D): HP-Hepatocyte; SS- sinusoidl; IC – Periportal infiltrates of inflammatory cells; H&E x 100

CHAPTER FIVE

DISCUSSION

This study was crafted to investigate the effects of Cinnamon bark extract on the histology of the liver of wistar rats. We explored varied doses of aqueous extract of Cinnamon bark on the livers the rats. The result obtained from this study showed that the extract activated inflammatory cells proliferation especially towards the portal area. This proliferation was dose dependent ranging from mild to severe inflammation of the liver. Most importantly, there were no observed degenerative changes in the liver hepatocyte.

Liver is the metabolic center of organism controlled by central nervous system. Its anatomic localization and specific tissue structure indicate its defensive role in organism. Approximately 80% of liver cells are hepatocytes. Non-hepatocytes include 40% endothelial cells 20% Kupffer cells, 20% lymphocytes, 20% stellate cells, and biliary cells. Natural killer cells make up 50% of liver population that reside in liver sinusoids (Wande *et al.,* 2019). The multitude of cells makes this organ play active role in peripheral immune tolerance of the organism using transforming growth factor-_ and haemopoetic cells. The fifth most common cancer in the world is liver cancer, 90% of which is hepatocellular carcinoma (HCC) 1 and the better understanding of liver's immunological processes will provide insight into the role of immune tolerance mechanisms and its contribution in the development of autoimmune diseases and chronic viral infections of liver.

Natural killer cells inhibit liver fibrosis, viral infection and tumor cells growth. The liver immune system is properly equipped with liver immune cells that achieve the critical task of protection against metastatic cells, pathogens, and foreign antigens by coordinating with anti-microbial components (inflammatory cytokines, chemokines, acute phase proteins, complement). Liver

plays its role as a buffer between systematic circulation and the contents of gut and about 80% of blood is supplied from gut into liver through portal vein. This blood is rich in harmless environmental antigens, microflora of gut, and dietary elements. Liver must endure immunogenic load by providing immunosurveillance for malignant cells and pathogenic infections.2,3 Innate immune cells of liver such as KCs, monocytes, dendritic cells (DCs), NK cells, natural killer T cells (NKT) cells, and neutrophils produce cytokine and initiate inflammation.4

As far as the histology studies were concerned, there was no degenerative changes in the hepatic tissues of the rats treated with Cinnamon bark extract in this study even though there were marked proliferation of inflammatory cells and this was exacerbated in the group receiving higher dose. Recent studies point to the potential certain extract to provoke inflammatory cell aggregating in the liver (Sulaiman *et al.,* 2015) even in liver cells of rats (Hussain et al., 2005). In agreement with our study, other studies reported toxic side effects on the liver tisssue, which subsequently impacted liver function (Vasanth and Kurian, 2017). The extract has also shown a significant ameliorative role in the antioxidant system in response to elevated levels of titanium dioxide nanoparticles or titanium dioxide bulk salt-induced oxidative stress with restoration of the histological damages in rat livers treated with titanium dioxide nanoparticles or titanium dioxide bulk salt (Shakeel *et al.,* 2017).

In conclusion, our findings revealed that the extracts from Cinnamomum caused did not cause any injury injury to liver of normal healthy rats. It is recommended that detailed immunological and electron microscopic evaluations of the tissues be carried out alongside other markers in the liver. (Biochemical assays for enzymes) in order to clearly establish specific alterations.

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