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ABSTRACT

Kaka bitters like other bitters is claimed to possess a number of folkloric therapeutic effects including lipid-lowering effects. However, there is no scientific data available as at the time of this study to evidence this claim. The Lipid-lowering effects of Kaka bitters were investigated by assessing it effects on the blood lipid parameters of wistar rats fed fat-enhanced diet. The was divided into three (3) groups: Group 1 rats was fed normal feed with distilled water; Group 2 was fed fat-enhanced diet with distilled water and Group 3 was fed fat-enhanced diet with Kaka bitters. The result obtained shows that blood TG levels decreased in group 3 rats compared with group 2, but the decrease is not statistically significant ($p < 0.05$). Also there was a statistically significant decrease in blood HDL levels and also statistically significant increase in total cholesterol and LDL levels of group 3 rats compared with group 2 ($p < 0.05$). The hyperlipidemic effect of Kaka bitters indicated by this result may be due to the alcoholic nature of Kaka bitters coupled with the antimicrobial effect of the bitters against the gut microbiota implicated in cholesterol metabolism and excretion. Kaka bitters is not a good therapy for treatment of dyslipidemia.

CHAPTER ONE

1.0 INTRODUCTION

Bitters as well as other medicinal plants have been the companions of man since time immemorial (Adaramoye, 2008). They occupy a central and integral place in modern herbal therapeutic medicine because of their efficacy and lesser toxicity compared synthetic drug. Many herbal remedies including bitters have been believed or known to be effective in management of dyslipidemia.

Dyslipidemia is a leading cause of coronary heart disease (CHD) and other related cardio- vascular disorders (CVDs). It is known that the occurrence of CHD is positively correlated with high total cholesterol and even more strongly with low density lipoprotein cholesterol. In contrast LDL Cholesterol, high level of HDL cholesterol has been associated with a decreased risk for heart disease (Clark *et al*, 2012). Efforts therefore have extensively been directed towards to reduce the risk of CVDs through the regulation of cholesterol (Adaramoye, 2008).

Kaka bitters like most other bitters is claimed to be an effective therapy for the management of abnormal blood lipid metabolism. However, there is a dearth of scientific data to support the folkloric use of this bitters in the treatment of abnormal lipid-related diseases (Adaramoye, 2008).

The present study therefore, was designed to provide scientific proof of the use of Kaka bitters in the management of dyslipidemia.

1.1 LITURATURE REVIEW

1.1.1 BITTERS – An Overview

1.1.1.1 HISTORY OF BITTERS

BIBLICAL VIEW

Mentions of herbal bitters with therapeutic effects were made in the Christian Holy Bible bitters. The Psalmist, king David talked about the “herb for the service of man… which strengthened man’s heart” (Psalm 104: 14, 15 KJV). Apostle Paul mentioned “wine (liquor) for thy stomach’s sake (i.e. aperitif, digestif, carminative, etc.) and thine own infirmities (who knows, may be antimicrobial, anti-genotoxic, astringent, diuretic or laxative involving infirmities) 1 Timothy 5:23. The name “bitters” to mean these drinks was used in

different bible passages including James 3:11.

CONTEMPORARY VIEW

It is in literature that the Angostura bitters was first compounded by a German physician, Dr. Johann Gottieb Benjamin Siegert in Venezuela in 1824 as a cure for sea sickness and had been discovered long before this. The bitter was reported to have effects of settling mild case of nausea, and also an apertif, digestive and carminative properties. The origin of herbal bitters has been tracked down to more than 5,000 years ago, possibly due to the opening of trade route with China (*Oyewo et al*, 2013b).

1.1.1.2 GENERAL MEDICINAL PROPERTIES OF BITTERS

Bitters generally are known to have

- Anti-inflammatory and antiedemateous properties
- Anti-HIV activity
- Anti bacterial and antifungal activities
- Anticancer and lymphocyte activation dual activities
- Immuno-stimulant activity (Botanical, 2013)
- Anti-oxidant activity
- Hepato protective activity
- Wound Heading activity
- Spasmolytic and spasmogenic dual activities
- Anti-viral activity (Sahu and pady, 2013)
- Insecticidal activity
- Heart inhibits
- Genotoxic and anti genotoxic dual activities (Banaraso *et al*, 2009).

1.1.1.3 CHEMISTRY OF BITTERS

Bitters are many from different herbal extract, many of these plants are from the plant family, Asteraceae, which often sesquiterpene lactones. The primary active ingredients in most bitters include saponin, tannin, flavonoid, etc. That of blessed thistle is a bitter tasting sesquiterpene lactone called cnicin (Alam *et al*, 2011). The bitter principles in artichoke, burdock and milk thistle for instance are flavonolignans. Other glycosides such as those from bitter-fasting flavonoid glycosides such as those from bitter orange peel including neohesperidin and naringin (Kareem *et al*, 2009).

1.1.1.4 MECHANISM OF ACTION OF BITTERS

Bitter generally use bitter taste to elicit their effects. They act on the tongue receptor where their effects are carried to the various area of the brain and further their signal they create are been interpreted and messages are appropriately sent out for their effect, for instance bitters elicit their effects as aperitifs by acting on the hypothalamus and increasing peristalsis.

There are fine distinct tastes that can be registered by the taste buds, viz: sally, sweet, bitter, sour, and umani or “savory”.

The bitter taste from bitters (a long sweet and umani taste) unlike salty and sweet bud taste which are sense by the taste bud through ion channels triggered by electronically charged particles, ions or certain food, are sensed by the taste bud through G-protein coupled receptors, a more sophisticated mechanism that is not well understand as that of ion channels. The compounds in bitters trigger certain molecules that close potassium ion channels, creating an action potential. Three cranial nerves are responsible for carrying the

action potential initiated in taste buds to brain, where taste is ultimately registered. The facial nerve carries signals from the front two-thirds of the tongue and the vagus from the soft platelet and epiglottis.

1.1.2 BLOOD LIPIDS

1.1.2.1 INTRODUCTION

Plasma lipid consist of triacylglycerol (16%), phospholipids (30%), cholesterol (14%), and cholesteryl esters (36%) and much smaller fraction of unesterified long-chain fatty acid (4%) (Murray *et al*, 2003). This later fraction the free fatty acid is metabolically the most active in plasma lipid (Murray *et al*, 2003). Blood lipids such as triglycerides, phospholipids, and cholesterol possess oil nature and are not soluble (or sparing soluble) in blood. They are found noncovalently to protein to form lipoprotein (Voet and Voet, 2011). Lipoproteins are spherical macromolecular complexes of lipids (cholesterol and phospholipid especially) with specific proteins called apoproteins or apolipoprotein (Champe *et al*, 2008; Pellery and Goldan, 2011). Lipoprotein are globular micelle-like particles that consist of nonpolar core of triacylglycerol and cholesteryl esters surrounded by an amphiphilic coating of protein, phospholipid and cholesterol (Voet and Voet, 2011). Macheboeut (1929) and Adair (1943) were the first people to work on lipoproteins. Plasma proteins are soluble in aqueous and weak salt solvents because of their protein components (Diribe *et al*, 1999).

1.1.2.2 GENERAL FUNCTIONS OF BLOOD LIPOPROTEINS

Blood lipoproteins have many functions including:

Function as transport vehicles for triacylglycerol and cholesterol to (and from) the body tissues (Voet and Voet, 2011; Champe *et al,* 2008).

Function to keep their component lipid soluble in as the transport them in the blood (Champe *et al*, 2008).

Lipoproteins function to maintain structural integrity of cell surface and subcellular particles like mitochondria and microsomes (Deb, 2011).

Lipoprotein changes in their plasma concentration in pathologies e.g. the -lipoprotein increases in severe diabetes mellitus, atherosclerosis etc. Hence determination of the relative concentration of - and - lipoprotein and pre--lipoprotein are of diagnostic importance (Deb, 2011).

1.1.2.3 TYPES OF BLOOD LIPIDS

Lipoproteins have been classified into five broad categories on the basis of their functional and physical properties (Voet and Voet, 2011). Classification depends on density (by ultra-centrifugation) or on the electrophoretic mobility (Vasudevan *et al*, 2011) or on composition, size,density and site of origin (Champe *et al*, 2008). These lipoproteins are chylomicrons, very low density lipoprotein, low density lipoprotein, high density lipoprotein and intermediate density lipoprotein (Voet and Voet, 2011; Vasudevan *et al*, 2011). Other blood lipids not included in classification of lipoprotein include free fatty acid, triglyceride and cholesterol.

1.1.2.4 CHYLOMICRON

Contains apolipoprotein B-48 (Vasudevan *et al*, 2011). They are rich in triacylglycerols and transport of lipids of dietary origin (Gurr and Harwood, 1991). Chylomicron are delipidated in the intestinal mucosal and secreted into the lacteals of lymphatic system (Vasudevan *et al*, 2011).

Large lipids especially those whose carbon chain number exceeds 14 carbons are too large to diffuse across capillary wall and are thus carried by chylomicrons. The later can not travel in blood either for its size, hence are secreted in lacteal (lymphatic capillaries) and travel through thoracic duct to enter systemic blood circulation at the left subclavian vein.

1.1.2.5 VERY LOW DENSITY LIPOPROTEIN (VLDL)

VLDL is also called pre-beta lipoproteins. They are rich in triacylglycerol but transport lipids of endogenous origin (Gurr and Harwood, 1991). VLDL has more protein, phospholipids and cholesterol than the chylomicrons. They are charged and migrate before the -globulins. For this reason are called the pre-globulins (Diribe *et al*, 1999). They are synthesized in the liver from glycerol and fatty acid and incorporated into VLDL along with hepatic cholesterol, apo-B-100, C-II and E. ApoB-100 is the major lipoprotein present in VLDL when it is secreted. Apo-E and C-II are obtained from HDL in plasma (Vasudevan *et al*, 2011).

1.1.2.6 INTERMEDIATE DENSITY LIPOPROTEIN (IDL)

Also broad bitter lipoproteins are major carriers of plasma cholesterol in man (Gurr and Harwood, 1991). Lipoprotein can be converted from one form to another. VLDL can give rise to an intermediate IDL by the loss of triacylglycerol (TAG) and Apo-C and subsequently from LDL (Deribe *et al,* 1999). IDL is richer in protein and poorer in cholesterol content than LDL (Deribe *et al,* 1999).

The lipoprotein lipase (LPL) found on the surface of endothelial cell lining removes the F.As of triacylglycerol in chylomicron and VLDL. The apo CII in the chylomicrons in the presence of Phospholipids activate LPL. The free fatty acids enter the cells, whereas the glycerol backbone of triglyceride is returned to the liver and kidney (via blood) where it is converted to DHAP, a glycolytic intermediate. During the process of fatty acid removal from chylomicrons, substantial portion of PL, Apo A and Apo C are transferred to HDL preventing further degradation VLDL or chylomicron by lipoprotein lipase.

1.1.2.7 LOW DENSITY LIPOPROTEIN (LDL)

Also called eta lipoprotein because they migrate with beta globulin . Its main apoprotein is B-100. LDL particles contain much less triglycerol than their VLDL predecessors, and have a high concentration of cholesterol and cholesteryl ester. LDL transport cholesterol from liver to peripheral tissues. The only apoprotein present in LDL is apo-B-100. Most of the LDL particles are derived from VLDL, but a small part is directly released from the liver. The half-life of LDL in the blood is about 2 days (Vasudevan *et al*, 2011).

1.1.2.8 HIGH DENSITY LIPOPROTEIN

HDL is formed from lipoprotein by the loss of ApoB in LDL (Diribe et al, 1999) .The major apoprotein in HDL are Apo-A1, with some Apo-A2, Apo-C and ApoE (Vasudevan et al, 2011). HDL serves as a transport reservoir of ApoC and ApoE which can be transferred to VLDL and chylomicrons and back (Vasudevan et al, 2011). Transport phospholipid and cholesterol from peripheral tissues to the liver (Diribe et al, 1999). In HDL-facilited lipid transport the excess cholesterol is taken to the liver for reprocessing (Gurr and Harwood, 1991). The intestinal cells synthesize component of HDL and release into blood. The nascent HDL in plasma is discoid in shape (Vasudevan et al, 2011).

1.1.2.9 FREE FATTY ACID

Or non-esterified fatty acid (NEFA) are complexed with albumin. Free fatty acids are not generally included in the classification of lipoprotein because they loosely bound to protein (Vasudevan et al, 2011). Free fatty acid help in the transport of lipid e.g. cholesterol (Diribe *et al*, 1999).

1.1.2.10 BIOCHEMICAL BASIS OF LIPOPROTEIN IMPLICATION IN PATHOLOGIES

Abnormal plasma concentrations of the different blood lipoproteins is implicated is many pathologies including atherosclerosis and coronary heart disease. In human the lipoprotein transport system is less perfect than in other animal and as a result human experience a gradual deposition of lipid – especially cholesterol in tissues (Champe *et al*, 2008). This is a potentially life-threatening occurrence when lipid deposition contributes to plaque formation, causing the narrowing of blood vessels (atherosclerosis)

(Champe *et al*, 2008). Polyanionic interaction like lipoprotein acid mucopolysaccharide complex have been implicated in human disease such as atherosclerosis and diabetes mellitus (Diribe *et al*, 1999). Since mucopolysaccharide are part of human connective tissues, they get involved in a number of reactions. The lipid acid mucopolysaccharide complex increase with increase in calcium concentration of the tissue (Diribe *et al*, 1999).

1.1.2 .11 IMPLICATION OF ABNORMAL LIPID PROFILE

High density lipoprotein (HDL) is believed to transport cholesterol away from tissues e.g. heart to the liver where it is removed from the body. It is thus known as “good cholesterol” good cholesterol of are made of little cholesterol and mostly protein. The LDL is on the other side known as “bad cholesterol” for its atherogenicity – it carries cholesterol away from the livers and deposits it in the arteries, which increases the risk of heart attack, stroke and other cardiovascular diseases.

Lipid profile therefore is important in ascertaining the body levels of the different lips, this may be necessary in knowing the risk of someone developing cardiovascular disease or for some other purpose e.g. to determine how effect an administered drug.

One can conclude on the implication of lipid profile by saying that it

Reveals abnormalities in lipid metabolism: DYSLIPIDEMIA e.g., HYPERLIPIDEMIA (following various disturbances of cholesterol and triglyceride levels).

The foregoing consequently is indicative of risk factors for cardio vascular diseases and also pancreatitis in rare occasions.

1.1.2.12 FACTORS AFFECTING LIPID PROFILE

Include among others:

age

lifestyle including diet, levels of physical activity, smoking

Sex

Genetics

Health including diabetic control

1.3 KAKA BITTERS

Kaka bitters is an uncommon Indian polyherbal medicine consisting of over 13 medicinal plants. According the manufacturer’s information it is a powerful blend of some premium quality herbs. We formulate for the removal of harmful toxins in the body, thereby supporting the immune system and body’s activity to resist disease.

COMPOSITION: Each 5ml Kaka bitters contains 40g of *Piper retrofractum*, 10g of *Butea monosperma,* 50g of *Swertia chirata,* 50g of Nardostachys jatamansi, 16g of Myristic fragrance, 50g of Bacopa monnieri, 50g of Embelia ribes, 20g of Apium graveolens, 50g of Holarrhena antidysenterica, 30g of Cassia angustiofolia, 75g of Azardirachata indica, 33g opf Aloe barbadensis and 15g of Cassia cinnamomum.

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