REVIEW OF LITERATURE

This chapter focuses on the survey of literatures related to phytochemical investigation of Scoparia dulcis L. along with a brief description of potential bioactivity evaluation of this plant.

2.1 Phytochemical investigation of Scoparia dulcis L.

The plant based food stock provides a diverse amalgamation of chemical components that are indispensable for human life which can contribute to the improvement of good health (Grusak, 2002). The phytochemical investigation of Scoparia dulcis L. as carried out so far, has afforded 71 compounds with varying structural skeletons. Literature review revealed that the plant is rich in terpenoids, flavonoids and steroids.

2.1.1 Terpenoids in Scoparia dulcis L.

The terpenoids constitute a large and diverse group of naturally occurring organic compounds which are the derivatives of five-carbon isoprene units and mostly multicyclic that vary in their functional groups as well as basic carbon skeletons. Plant terpenoids are used extensively for their aromatic qualities and play a vital role in traditional herbal remedies.

Till date, 25 terpenoids have been reported from Scoparia dulcis L. The tetracyclic diterpenoids such as scopadulcic acid A (i), scopadulcic acid B (ii) and dulcinol/scopadulciol (iii) were isolated as the first members of labdane-derived diterpenoids named scopadulane. Further efforts led to isolation of three new natural metabolites viz., 4-epi-scopadulcic acid B (iv), dulciol (v) and iso-dulcinol (vi) from Bangladesh. Using systematic extraction and isolation procedure scopadulcic acid C and nine other known compounds were isolated from Vietnam. Moreover, two more terpenoids viz., lupeol (vii), betulinic acid (viii) (Phan et al., 2006) and scopadulcic acid
B and its debenzoyle derivative, diacetyl scopadol (ix) having gastric ATPase activity have also been reported from this plant (Asano et al., 1990).

Bioassay-directed fractionation of 70% ethanol extract led to the isolation diterpene acids *viz.*, scoparic acid A (x), scoparic acid B (xi), scoparic acid C (xii) and scoparic acid D (xiii) (Hayashi et al., 1992; Latha et al., 2009). A novel aphidicolane-type diterpene, scopadulin (xiv) was isolated from acetone extract of this herb (Hayashi et al., 1990). The diterpenes *viz.*, scoparinol, dulcidion, scopanolal and triterpenes *viz.*, glutinol and dulcioic acid were reported from this plant where scoparinol and glutinol demonstrated significant analgesic and anti-inflammatory activity in animals (Ahmed et al., 2001; Freire et al., 1993; Ahsan et al., 2003; Technical data report for vassourinha Scoparia dulcis, 2002). The chemistry and biological activity study of this herb led to the isolation of friedelin (xv), 6-amyrin (xvi) and iffloxic acid (xvii) (Mahato et al., 1981) and a chemotype, 6-benzoyl-labda-8(17), 13-diene-15, 18-diol was also reported in Taiwan, China and Thailand which was characterized by the presence of scopadulciol and scopadiol (xviii) (Hayashi et al., 1993).

![Scopadulcic Acid A](image1.png) ![Scopadulcic Acid B](image2.png) ![Scopadulciol](image3.png)

Scopadulcic Acid A  Scopadulcic Acid B  Scopadulciol
2.1.2 Flavonoids in *Scoparia dulcis* L.

Flavonoids are the group of plant secondary metabolites having structure similar to that of flavone and are the most common group of polyphenolic compounds found ubiquitously in plants. They possess a broad range of biological activities such as antioxidants, antidiabetic and phytoestrogens and can modify the activities of key cell-signalling enzymes, such as tyrosine kinases, phosphodiesterases and phosphoinositide kinases (Sharma and Shah, 2010).

Till date, 26 flavonoids have been isolated from *Scoparia dulcis* L. Three acetylated flavonoid glycosides *viz.*, 5, 6, 4-trihydroxyflavone 7-O-α-L-2,3-di-O acetylRhamnopyranosyl-(1→6)-β-D-glucopyranoside, apigenin 7-O-α-L-3-O acetylRhamnopyranosyl-(1→6)-β-D-glucopyranoside, apigenin 7-O-α-L-2,3-di-O acetylRhamnopyranosyl-(1→6)-β-D-glucopyranoside and eugenyl β-D-glucopyranoside (xix) were isolated from this plant. Compounds such as apigenin 7-O-α-L-3-O acetylRhamnopyranosyl-(1→6)-β-D-glucopyranoside and apigenin 7-O-α-L-2, 3-di-O-acetylRhamnopyranosyl-(1→6)-β-D-glucopyranoside showed an enhancing activity of nerve growth factor-mediated neurite outgrowth in PC12D cells (Li *et al.*, 2004). Another flavone, cirsitakaoside (xx) showed mutagenic effect (Pereira-Martins *et al.*, 2013).
1998) and flavone glycoside 5,7,8,3’,4’,5’-hexahydroxylavone glucuronide and isovitexin showed inhibitory activity against β-glucuronidase (Kawasaki et al., 1988).

Phytochemical investigation of ethanol extract of the whole plant has resulted in the isolation of hispidulin (xxi) (Osei-Safo et al., 2009). The flavonoids, 7-O-methyl scutellarein and 3-4, 5-5-7-8 hexahydroxylavone (Praveen et al., 2009), the flavones, acacetin (xxii) (Hayashi et al., 1993), 4, 5-dihydroxy-3, 7 dimethoxyflavone, 3-hydroxy-4, 5, 7-trimethoxyflavone (Phan et al., 2006), 3-4-5-5-7-8 hexahydroxy 7-o-beta-d-glucuronide and Scutellarin methyl ester (Presence of compounds in vassourinha Scoparia dulcis, 2004) were isolated from this herb where acacetin showed dose-dependent inhibition of viral replication (Hayashi et al., 1993). From India, a flavone, scutellarein 7-o beta-d-glucuronide has been reported from leaf extract of this plant (Presence of compounds in vassourinha Scoparia dulcis, 2004). Other flavonoids viz., apigenin (xxiii), cirsimarin (xxiv), cynaroside (xxv), hymenoxin, linarin (xxvi), luteolin (xxvii), scutellarein (xxviii), scutellarin (xxix), vicenin (xxx), and vitexin (xxxi) were also reported from this plant (Technical data report for vassourinha Scoparia dulcis, 2002).

![Chemical structures](image)

eugenyl beta-D-glucopyranoside  
cirsitakaoside  
hispidulin

(xix)  
(xx)  
(xxii)
Fig 2.2: Structures of a few flavonoids isolated from Scoparia dulcis L.
2.1.3 Steroids in *Scoparia dulcis* L.

Steroids are group of secondary metabolites where all plant steroids are hydroxylated at C-3 and are sterols. Till date, five steroids have been isolated from this plant.

Phytochemical investigation of ethanol extract of the whole plant of *Scoparia dulcis* L. has resulted in the isolation of a steroidal glycoside, β-sitosterol-β-D-glucoside (Osei-Safo *et al.*, 2009) and steroidal compounds *viz.*., daucosterol (xxxii), stigmasterol (xxxiii) and taraxerol (xxxiv) were also isolated of Bangladeshi origin. From India and Bangladesh, another sterol, β- sitosterol (xxxv) has been isolated from root bark and whole plant respectively (Presence of Compounds in Vassourinha *Scoparia dulcis*, 2004).

![Daucosterol](xxxii) ![Stigmasterol](xxxiii) ![Taraxerol](xxxiv)

![Sitosterol](xxxv)

**Fig 2.3:** Structures of a few steroidal compounds isolated from *Scoparia dulcis* L.
2.1.4 Some other compounds present in *Scoparia dulcis* L.

Apart from all the above categories, some other phytochemicals have also been reported from *Scoparia dulcis* L. belonging to different groups such as carbohydrate, heterocyclic compounds, phenolic compounds, benzoic compounds, catecholamines, glycosides and sugar alcohols.

From India, an antidiabetic compound amellin was isolated and characterized by Nath (1943). Moreover, adrenalin (xxxvi), 6-methoxybenzoxazolinone, nirtetralin (xxxvii) and niranthin were isolated and analysed by spectroscopic data (Phan et al., 2006). The nitrogenous heterocyclic compounds such as, benzoxazolin-2 one, 6-methoxy from callus tissues from Japan, benzoazin-3-one,1-4: 2(h): 2 hydroxy and benzoazolone,2-3(h): 6-methoxy were isolated from aerial parts of *Scoparia dulcis* L. of Vietnamese origin (Presence of compounds in vassourinha *Scoparia dulcis*, 2004). This plant is also reported to contain benzoazin (xxxviii), benzoazolin, benzoxazolinone, coixol (xxxix), coumaric acid (xl), mannitol (xli) and gentisic acid (Technical data report for vassourinha *Scoparia dulcis*, 2002).

![Image of Adrenalin](image)

**Adrenalin**

![Image of Nirtetralin](image)

**Nirtetralin**

![Image of Benzoazin](image)

**Benzoazin**

(xxxvi)  

(xxxvii)  

(xxxviii)
Fig 2.4: Structures of different group of compounds isolated from *Scoparia dulcis* L.

2.2 Potential bioactivity evaluation of *Scoparia dulcis* L.

Literature scrutinization revealed the potential medicinal efficacy of the plant extract(s)/pure chemical constituent(s) against various ailments, experimented both *in vivo* and *in vitro* studies. Brief accounts of such efficacy are listed below:

2.2.1 Antacid and antiulcer activity

The aqueous extract of the aerial parts of this plant was found to be gastro protective in rodent model. This also established the inhibition of histamine or betahanechol-stimulated gastric secretion in pylorus-ligated mice with related effectiveness suggesting inhibition of the proton pump. The aqueous extract was also found to inhibit acute gastric lesions induced in rats by indomethacin (Mesia-Vela *et al.*, 2007). A tetracyclic diterpenoid, scopadulciol, mildly inhibited hog gastric H+, K(+)-ATPase. The inhibitory activities of derivatives of scopadulcic acid B, including scopadulciol, markedly enhanced the inhibitory activity, while debenzylation reduced the activity (Hayashi *et al.*, 1991). The aqueous extract from aerial parts of the plant inhibited the indomethacin-induced gastric damages in rats (Babincova *et al.*, 2008). These results
collectively validate pharmacologically the popular use of *Scoparia dulcis* L. in gastric disturbances as an antacid and antiulcer agent in traditional medicine.

### 2.2.2 Analgesic, anti-inflammatory and antipyretic activity

The analgesic, anti-inflammatory and antipyretic activities of the aqueous and ethanol extracts of *Scoparia dulcis* L. were demonstrated in rodent models (mice and rats) (Freire *et al.*, 1993). Both extracts prolonged the sleeping time induced by pentobarbital in mice where ethanol extract was more effective than aqueous extract. Ethanol extract also reduced writhing induced by acetic acid in mice. Glutinol, a major triterpene produced the same effect. The plant extract and glutinol reduced the paw edema and pleurisy induced by carrageenan in rats, but only ethanol extract reduced the paw edema induced by dextran or histamine. These results indicated that the plant was endowed with analgesic and anti-inflammatory activities which were mainly associated with the presence of glutinol and flavonoids that exerted their action in the early phase of acute inflammatory process (Freire *et al.*, 1993). The diterpene scoparinol also demonstrated significant analgesic and anti-inflammatory activities in animals (Ahmed *et al.*, 2001).

### 2.2.3. Cytotoxic activity

Four diterpenes *viz.*, iso-dulcinol, 4-epi-scopadulcic acid, dulcidion and scopanolal, isolated from aerial parts of the plant demonstrated significant cytotoxic activity (Ahsan *et al.*, 2003). In another study, diterpenoid scopadulcic acid B showed more cytotoxicity against cell lines derived from tumor tissues compared to cell lines from normal tissues (Hayashi *et al.*, 1992). A scopadulane-type diterpenoid, scopadulcic acid C showed significant cytotoxic assay on human epidermoid carcinoma KB cells (Phan *et al.*, 2006).
2.2.4. Antitumor activity

The tetracyclic diterpenoid, scopadulcic acid B (SDB) was found to be active in inhibition of tumor promoter studied in vitro and in vivo. It prevented TPA-enhanced phospholipid synthesis in cultured cells and also suppressed the promoting effect of TPA on skin tumor development in mice. The effectiveness of SDB was stronger than that of other natural antitumor-promoting terpenoid (Nishino et al., 1993). The diterpene, scopadulcic acid C increased the efficacy of antitumor activity of acyclovir and ganciclovir in HSV-TK gene therapy which was due the activation of viral thymidine kinase (Nkembo et al., 2005; Nakagiri et al., 2005).

2.2.5. Antidiabetic activity

Scoparia dulcis L. has been used as a traditional remedy for diabetes mellitus in India and Nigeria (Okhale et al., 2010). To understand the mechanism by which the plant alleviates hyperglycemia, the following studies were performed. The administration of SPEt (Scoparia dulcis L. plant extracts) considerably lowered the blood glucose level with significant rise in plasma insulin level in streptozotocin diabetic rats. SPEt exhilarated the stimulation of insulin secretion from isolated pancreatic islet cells specified its insulin secretagogue activity (Latha et al., 2004). Flow cytometric assessment established the effect of SPEt which supressed the STZ-induced intracellular oxidative stress in RINm5F cells (Latha et al., 2004). The efficacy of plant was also studied in streptozotocin diabetic rats on derangement in glycoprotein levels. Oral administration of SPEt to diabetic rats showed decreased levels of blood glucose and plasma glycoproteins. It demonstrated an increase level of plasma insulin and tissue sialic acid while the levels of tissue hexose, hexosamine and fructose were close to normal. This indicated the potential beneficial effect of Scoparia dulcis L. on glycoproteins beside its antidiabetic effect (Latha and Pari, 2005).
The effect of aqueous extract on glucose uptake activity and the Glut 4 translocation constituents in L6 myotubes in comparison to insulin was studied. The plant showed the potential to be considered as a hypoglycaemic plant based on its good glucose transport properties (Beh et al., 2010). Again, the plant extracts were studied for prevention and management of diabetes mellitus induced experimentally by streptozotocin injection. Oral administration of aqueous extract to diabetic rats showed significant increase in plasma insulin and plasma antioxidants and a significant decrease in lipid peroxidation (Pari and Latha, 2004).

The experiment conducted on hepatic key metabolic enzymes of carbohydrate metabolism in STZ-induced diabetic rats, aqueous, ethanol and chloroform extracts were orally administered after which the metabolic enzymes were assayed. Aqueous extract demonstrated better result than the rest which indicated the hypoglycaemic effect by regulating the above biochemical modifications in streptozotocin diabetes (Pari and Latha, 2005). The effect of aqueous extract on the polyol pathway and lipid peroxidation was studied and compared with glibenclamide. This might have been the results of reduced influx of glucose into the polyol pathway that lead to increase activities of plasma insulin and antioxidant enzymes and decreased activity of sorbitol dehydrogenase (Latha and Pari, 2004). The antihyperglycaemic effect of diterpenoid scoparic acid D (SAD) showed a decreased level of glucose as compared to diabetic control rats. The effect of SAD on STZ-treated rat insulinoma cell lines (RINm5F cells) and isolated islets in vitro evoked two-fold stimulation of insulin secretion from isolated islets, indicating its insulin secretagogue activity (Latha et al., 2009).

Oral administration of aqueous extract of *Scoparia dulcis* L. to streptozotocin diabetic rats led to a substantial reduction in blood glucose, serum and tissue cholesterol, triglycerides, free fatty acids, phospholipids, 3-hydroxy-3-methylglutaryl (HMG)-CoA
reductase activity, very low-density lipoprotein and low-density lipoprotein cholesterol levels (Pari and Latha, 2006). Again, the same extract of leaves observed a considerable decrease in blood glucose, glycosylated haemoglobin and an increase in total haemoglobin. In an oral glucose tolerance test performed in experimental diabetic rats resulted a significant improvement in glucose tolerance in animals treated with leaf extract which was comparable to that of glibenclamide (Pari and Venkateswaram, 2002). The hypoglycaemic effect of flavonoids from methanol extract of aerial parts in normal, glucose loaded and streptozotocin induced diabetic rats showed significant hypoglycaemic activity when compared with glibenclamide. The hypoglycaemic effect was due to increase uptake of glucose at tissue level and increase function of pancreatic β-cell or inhibition of intestinal absorption of glucose (Sharma and Shah, 2010). Hence, the above studies may establish promising therapeutic potential of Scoparia dulcis L. for better control, administration and prevention of diabetes mellitus progression.

2.2.6 Antioxidant activity

Antioxidants have been used as a significant defensive agent for human health. The antioxidant effect of aqueous extract of Scoparia dulcis L. resulted in significant decrease in blood glucose and formation of free radical in tissues while increase in plasma insulin. The antioxidant property of the plant was associated with decrease in thiobarbituric acid reactive substances (TBARS) and hydroperoxides (HPX) and increase in the actions of superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), reduced glutathione (GSH) and glutathione-S-transferase (GST) (Pari and Latha, 2005). The phenolic compounds existing in the plant leaf extract exhibited antioxidant property as revealed by the total antioxidant activity, DPPH radical scavenging activity and reducing power (Pari et al., 2007). The potential antioxidant property of aqueous extract of Scoparia dulcis L. when investigated in rats
exposed to cadmium, it resulted reduced superoxide dismutase activity while considerably increasing catalase activity and malondialdehyde levels in the liver and kidney. These observations showed the antioxidant possessions of aqueous extract, enough to mitigate against free radical induced oxidative stress in experimental cadmium intoxication in the rat (Adaikpoh et al., 2007). The extract also showed in vitro antioxidant activity (Patnibul et al., 2008). Antioxidant activity of the same extract when investigated in vitro by thiobarbituric acid reactive substances (TBARS) assay based on fowl egg yolk, showed marked and dose-dependent antioxidant activity (Ratnasooriya et al., 2005).

The effect of aqueous extract of SPEt on level of oxidative damage as well as antioxidant defence system in the brain of STZ diabetic rats was investigated. Oral administration of SPEt and glibenclamide to diabetic-induced rats suggestively reduced the blood glucose level and increased the plasma insulin level close to normal. The levels of lipid peroxidation markers viz., TBARS and hydroperoxides in the brain were significantly reduced suggesting antioxidant potential that may be used for therapeutic purposes (Pari and Latha, 2004). The scavenging capabilities of the extract for 1-diphenyl-2-picrylhydrazyl and hemoglobin-catalyzed linoleic acid peroxidation with an oxygen electrode demonstrated strong antioxidant activity corresponding to mitigation of the generation of hydroxyl radicals, a potential basis for the observed therapeutic effects of this weed (Babincova and Sourivong, 2001).

2.2.7 Antimicrobial and antifungal activity

The antibacterial activities of 4-epi-scopadulcic acid B, dulcidiol, iso-dulcinol and scopadulcic acid C against Escherichia coli, Bacillus subtilis, Staphylococcus aureus, and methicillin-resistant Staphylococcus aureus as well as antifungal activity against Candida albicans were well reported (Phan et al., 2006). Various concentrations of
chloroform and methanol fractions against different bacterial and fungal strains showed significant antimicrobial and antifungal activity compared to respective reference drugs (Latha et al., 2006).

### 2.2.8 Antiviral activity

The diterpenoids isolated from *Scoparia dulcis* L. were studied *in vitro* against herpes simplex virus type 1 in a hamster test model where scopadulcic acid B was found to inhibit viral replication by interfering with considerably early events of virus growth as indicated by single-cycle replication experiments (Hayashi et al., 1988). The compound scopadulciol showed stimulatory effects on the antiviral potency of acyclovir or ganciclovir (Hayashi, 2008). The effect of acacetin isolated from *Scoparia dulcis* L. on herpes simplex virus type 1 was studied *in vitro* showed to be the most potent agent and caused dose-dependent inhibition of virus replication (Hayashi et al., 1993). Scopadulin, a novel aphidicolane-type diterpene have been reported to possess antiviral activity (Hayashi et al., 1990). Aqueous and methanol extracts of leaf were screened against human immunodeficiency virus (HIV) type-1 reverse transcriptase (RT) activity. In this study, methanol extract showed remarkable HIV type-1 reverse transcriptase inhibitory activity comparable to that of zidovudine (Porika et al., 2009). The compound hispidulin isolated from ethanol extract was found to be inactive against HIV-1/IIIB in MT-4 cells in Tetrazolium-based colorimetric selective assay while in aqueous extract the same test was found positive (Osei-Safo et al., 2009).

### 2.2.9 Antimalarial activity

This medicinal herb also found to possess antimalarial activity. The diterpenoid scopadulcic acid A possessed potential against various *Plasmodium falciparum* isolated with an IC$_{50}$ of 27 mcM against D$_6$ clone (African Sierra isolate) and an IC$_{50}$ of 19 mcM against W$_2$ clone (Indochina isolate) (Riel et al., 2002).
2.2.10 Hepatoprotective activity

*Scoparia dulcis* L. has been traditionally used as remedy for many liver ailments. Liver cirrhosis represents the common pathological outcome for the majority of chronic liver problems. The hydroalcoholic extract of the plant displayed significant hepatoprotective property against CCl₄ induced liver damage in rats which was due to their free radical scavenging ability. The *in vivo* hepatoprotective activity of HASD extracts demonstrated a significant defensive action against CCl₄ induced changes in serum glutamate oxaloacetate transaminase (SGOT), glutamate pyruvate transaminase (SGPT), serum alkaline phosphatase (ALP), total bilirubin and an increased level of total protein and on liver histopathology when compared to positive control (Sahoo and Madhavan, 2009). Again, hepatoprotective activity of petroleum ether, diethyl ether and methanol extracts against CCl₄ induced acute liver injury in mice indicated the potential hepatoprotective activity of PDM extract, which may be attributed to free radical scavenging activity of terpenoid constituents (Praveen *et al.*, 2009).

2.2.11 Neurotrophic activity

The acetylated flavone glycosides isolated from *Scoparia dulcis* L. showed to possess NGF-promoting activity to treat neurological disorders. The acetylated flavonoid glycosides apigenin 7-O-alpha-L-3-O-acetylhamnopyranosyl-(1-->6)-beta-D-glucopyranoside and apigenin 7-O-alpha-L-2,3-di-O-acetylhamnopyranosyl-(1-->6)-beta-D-glucopyranoside, showed an enhancing activity of nerve growth factor-mediated neurite outgrowth in PC12D cells (Li *et al.*, 2004). Methanol extract of this plant from Paraguay and Thailand also showed enhanced neurite outgrowth induced by NGF from PC12D cells (Li and Ohizumi, 2004).
2.2.12 Antihyperlipidemic activity

The antihyperlipidemic activity of *Scoparia dulcis* L. with streptozotocin-induced experimental diabetic rats resulted a significant reduction in blood glucose, serum and tissue cholesterol, triglycerides, free fatty acids, phospholipids, 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase activity and very low-density lipoprotein and low-density lipoprotein cholesterol levels. The decreased serum high-density lipoprotein cholesterol, anti-atherogenic index and HMG-CoA reductase activity in diabetic rats were found reversed towards normalization after the treatment. The administration of SPEt to normal animals resulted in hypolipidemic effect. The results indicated the antihyperlipidemic activity of normal and experimental diabetic rats when compared to standard drug (Pari and Latha, 2006).

2.2.13 Mutagenic activity

The mutagenic activity of the flavone cirsitakaoside extracted from this medicinal herb was evaluated *in vitro* by using human peripheral blood cultures. The compound established to be mutagenic at the highest concentration tested (15 μg/ml) (Pereira-Martins *et al*., 1998).

2.2.14 Gastro Intestinal activity

The plant was also found to possess significant gastro intestinal activity. The diterpenoid scopadulcic acid B and it’s debenzoyl derivative, diacetyl scopadol (DAS) involved in inhibition of K+-dependent dephosphorylation of proton pump for gastric acid secretion. Both the compounds also dose-dependently and specifically inhibited ATP hydrolysis by gastric H+K-ATPase. Regarding activation of cation K+, scopadulcic acid B was treated as mixed inhibitor, whereas DAS as an uncompetitive inhibitor which differed from the irreversible inhibitor omeprazole (Asano *et al*., 1990).
2.2.15 Other pharmacological activities

*Scoparia dulcis* L. is recognized to possess several other pharmacological activities which ensure the usage of the plant for various conditions. In an *in vivo* study, aqueous extract revealed the presence of two catecholamines, noradrenaline and adrenaline which accounted for the hypertensive and inotropic effects after parenteral administration (Freire *et al.*, 1996). A major effect on the onset and duration of sleep was initiated by scoparinol on pentobarbital-induced sedation in animals. In another study, sleeping time induced by sodium pentobarbital was prolonged 2-fold in mice pretreated with ethanol extract. Scoparinol possessed significant diuretic action as revealed by the amount of urine volume after administration (Ahmed *et al.*, 2001). The flavone glycoside isovitexin showed inhibitory activity against β-glucuronidase (Kawasaki *et al.*, 1988). The effect of *Scoparia dulcis* L. on *Trypanosoma brucei* induced anaemia was investigated which indicated a significant decrease in PCV, Hb concentration and RBC. However, the severity was significantly less pronounced in the infected rabbits that were treated with *Scoparia dulcis* L., compared to their infected but untreated counterparts (Orhue and Nwanze, 2009). Again, the effect of orally administered plant extract on *Trypanosoma brucei* induced changes in serum total protein, albumin and globulin were investigated in rabbits over a period of twenty eight days. The infection resulted in hyperproteinaemia, hyperglobulinaemia and hypoalbuminaemia. However, these lesions were less severe in the infected and treated group comparative to their untreated counterparts. It was speculated that the herb might be associated in modulating the severity of trypanosome related lesions by some however indeterminate mechanisms (Orhue *et al.*, 2005).
2.3 Computer Aided Drug Design and Natural products

Natural product based drug discovery always has a successful history. For further advancement of the documentation of novel drugs from compounds of natural origin, natural product research is progressively being combined with computer-aided drug design techniques that have made major contributions to different stages of drug discovery. Successful contributions of CADD to natural product research have been achieved by the development of number of software, databases and online tools accessible for medicinal chemists, biologists and researchers (Liao et al., 2011). Traditionally, identifying active compounds from natural products depend on the experimental estimation in a set of biological assays available. Despite this method has given rise to the successful identification of lead molecules and approved drugs, it is expected that the incorporation of computational approaches with experimental-based natural product research will increase the success rate. The first development was in the mid-1980s and the first successful stories of computer-aided rational design of peptide-based HIV-proteinase inhibitor was published in early 1990s (Erickson et al., 1990; Adam et al., 2002). Later, Barlow et al. studied the integration of in silico approach with Chinese herbal medicine’s research (Barlow et al., 2012).

Large quantities of natural products are biologically active and have favourable ADME/Tox (absorption, distribution, metabolism, excretion, and toxicology) properties (Quinn et al., 2008). Modern drug discovery approach often resort to natural sources to direct careful design of “drug-like” leads by synthetic modifications of the latter (Newman, 2008; Harvey, 2008). Nowadays, computer-aided drug design (CADD) methods with the integration of the virtual screening (VS) of large compound databases against authenticated drug targets followed by the cautious selection of virtual hit compounds screened by biological assays, has become a very essential part of the drug
discovery process. This approach substantially constricts the number of compounds that undergo biological screening and hence considerably cuts down the cost of discovery of a drug (Harvey, 2008). The past era has seen the development of a number of natural product compound databases viz., the Chinese traditional medicinal herbs database (Qiao et al., 2002), the SuperNatural database (Dunkel et al., 2006), the NAPROC-13 database (López-Pérez et al., 2007), Marine natural products databases (Lei and Zhou, 2002; Blunt et al., 2004), the Thai medicinal plants database PHARM (Sangma et al., 2005) and a database of pharmacophoric features of compounds isolated from medicinal plants in India (Daisy et al., 2011; Pitchai et al., 2010).

The African flora and the Congo Basin hold a huge potential as a source of drugs, headed the establishment of the Department of Organic Chemistry at the University of Yaoundé, whose natural product research team have been dynamically involved in the separation and characterization of active principles from medicinal plants that could serve as drug leads. The CamMedNP can be used in CADD for pharmacophore mining, protein-ligand docking, VS against validated drug targets and substructure searching (Efange, 2002).

The publicly available large compounds databases viz., PubChem, ChEMBL and Binding Database are annotated with biological activity (Nicola et al., 2012). Yongye and Medina-Francisco compiled a list of five natural products databases which contain 560 to 89000 compounds and the numbers are growing (Yongye et al., 2012). The large and commonly used databases viz., ZINC database (Irwin and Shoichet, 2005), the Traditional Chinese Medicine database (Chen, 2011) and the Universal Natural Products Database (UNPD) (Gu et al., 2013) are sources of natural products freely available online.
Molecular modeling approach is increasingly used to propose binding models of bioactive natural products with their molecular targets. This has been helpful in further understanding the bioactivity of the compounds and to direct the chemical synthesis of natural product analogues with enhanced activity. Target fishing approaches have also been used to recognize potential molecular targets of natural products. Thus, the continuous integration of experimental natural products research with computer aided drug design is anticipated to further advance the drug discovery process (Medina-Franco, 2013).