

ABSTRACT

Chemical Characterization
and Selected Biological Evaluation
of some Naturally Occurring Limonoids
and their Semi-Synthetic Derivatives

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This dissertation gives a description of the isolation, characterization and identification of six naturally occurring limonoids namely, swietenolide (**I**), 3,6-O,O-diacetylswietenolide (**II**), swietenine (**III**), swietemahonin G (**IV**) and augustineolide (**XXX**) of *Swietenia macrophylla* and 2-hydroxyswietenine (**V**) of *Swietenia aubrevilleana* (**CHAPTER TWO**); followed by details of the preparation, characterization and identification of derivatives **VI** - **XVII** (acylation of **I**), **XVIII** (alkaline hydrolysis of **I**), **XIX** (acylation of **III**), **XX** (hydrolysis of **III**), **XXI** (methylation of **XX**), **XXII** - **XXIV** (acylation of **XXI**), **XXV** (hydrolysis of **V**), **XXVI** (methylation of **XXV**), **XXVII** - **XXVIII** (acylation of **XXVI**) and **XXIX** (hydrolysis followed by methylation of **IV**) in **CHAPTER THREE**; culminating in a study of the effect of some of these compounds in selected bioassays (**CHAPTER FOUR**). **CHAPTER ONE** outlined the structural diversity of some naturally occurring limonoids of the order Rutales and suggested biogenesis, along with an overview of the biological activities seen in limonoids.

Antifeedant Index (AI) values were recorded for twenty-eight compounds (**I - XIII, XV, XVII - XXX**) tested against the fourth instar larvae of *Spodoptera frugiperda* at 1000, 500, 250, 125 and 62.5 ppm. Swietenine (**III**) showed the highest AI (> 94%) at all concentrations studied. 3-O-isobutyrylswietenolide (**XV**) was the most effective semi-synthetic derivative at 62.5 ppm (AI 93.53%). 3-O-acetoxyacetylswietenolide (**XII**) was the most effective semi-synthetic derivative at concentrations above 62.5 ppm. Both **XV** and **XII** were more effective than **I**. 3,6-O,O-dibenzoyl-3-detigloylisoswietenine (**XXIII**) was found to be a phagostimulant. It was observed that a free 6-OH and an acyl substituent at the C-3 position were important in order to obtain high AI values against *Spodoptera frugiperda*. Substituting both the 3-OH and 6-OH with a benzoyl group caused low AI values.

Feeding Inhibition Index (FII) values were obtained for twenty-six compounds (**I - V, VII, IX - XIII, XV, XVII - XXX**) against the neonate larvae of *Helicoverpa zea*, *Heliothis virescens* and *Manduca sexta* at 250 ppm. Swietenolide (**I**), containing a 3-OH and 6-OH, was the only compound that showed moderate FII values against all the three species studied (FII 48.25 %, 68.02% and 46.26%, respectively).

Twenty-eight compounds (**I - XIII, XV, XVII - XXX**) tested against *Artemia salina* at concentrations ranging from 400 to 1 ppm revealed that 3-O-benzoyl-3-detigloylisoswietenine, **XXII** (LC₅₀ 3.88 ppm) was the most toxic compound. The presence of a benzoyl substituent was important for high toxicity levels.

Twenty-six compounds (**I - V**, **VII**, **IX - XIII**, **XV**, **XVII - XXX**) at 10 μ M were studied for antioxidant activity. The most effective compounds were detigloylisowietenine (**XXI**) and demethyl-3-detigloyl-2-hydroxyisowietenine (**XXV**), which were more effective than the synthetic antioxidants used (BHA, BHT and TBHQ). The results showed that increasing the number of hydroxyl groups (detigloylation or demethylation) increased antioxidant efficacy.

In antimicrobial assays against the *Pseudomonas aeruginosa*, *Escherichia coli*, *Staphylococcus* species, *Streptococcus* species, *Salmonella* species, *Aspergillus niger*, *Aspergillus flavus* and *Penicillium* species no activity was observed for the compounds studied (**I - VIII**, **XV** and **XVII - XXX**) at concentrations up to 1000 ppm.

No anti-inflammatory activity was observed for compounds (**I - V**, **VII**, **IX - XIII**, **XV**, **XVII - XXX**) studied at concentrations up to 100 ppm in cyclooxygenase I and II assays.

When applied in mosquitocidal assays at 250 ppm using the fourth instar larvae of *Ochlerotatus triseriatus* 100 % mortality was recorded for the 6-O-benzoylswietenolide (**VII**), 3,6-O,O-dipropionylswietenolide (**IX**), 3-O-isovalerylswietenolide (**XIII**), 3-O-isobutyrylswietenolide(**XV**) and 3,6-O,O-di-*tert*-butylacetylswietenolide (**XVII**). It was observed that the $\Delta^{8,14}$ bond was important for high toxicity.

Key words: Structural diversity, natural limonoids, semi-synthetic limonoid derivatives, antifeedant, toxicity, antioxidant.