ANTI-DIABETIC ACTIVITY OF CHEMICAL CONSTITUENTS ISOLATED FROM *Kopsia teoi* AND *Catharanthus roseus* (APOCYNACEAE), AND CORROSION INHIBITION STUDIES OF ITS EXTRACTS

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by

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T	Absolute temperature (in kelvin)
E_a	Activation energy
K_{ads}	Adsorption equilibrium constant
α	Alpha
Å	Angstrom
ω	Angular frequency
βa	Anodic Tafel constant
N	Avogadro's constant
β	Beta
br	Broad
C	Carbon
^{13}C	Carbon NMR
βc	Cathodic Tafel constant
cm	Centimeter
ΔH	change in enthalpy
R_{ct}	Charge transfer resistance
δ_C	Chemical shift carbon
δ_H	Chemical shift hydrogen
χ^2	Chi-square
IC_{50}	Concentration required to inhibit 50% of activity
R^2	Correlation coefficient
i_{corr}	Corrosion current density
E_{corr}	Corrosion potential
CR	Corrosion rate

J	Coupling constant
°C	Degree Celcius
C_{dl}	double-layer capacity
eV	Electron volt
ΔS	entropy change
Fe^{3+}	Ferric
Fe^{2+}	Ferrous
g	Gram
Hz	Hertz
h	Hour
H	Hydrogen
^{1}H	Hydrogen NMR
|Z|	Impedance modulus
IE	Inhibition efficiency
Fe	Iron
kg	Kilogram
λ	Lambda
m/z	Mass to charge ratio
MHz	Megahertz
m	Meter
µM	Micromolar
mpy	Milli per year
mV	Milli volt
mg	Milligram
mL	Milliliter
mm	Millimeter
min	Minute

M	Molar
nm	Nanometer
Ω cm^2	Ohm’s centimeter square
O	Oxygen
ppm	Parts per million
cm^{-1}	Per centimeter
%	Percent
π	Pi
h	Planck constant
A	Pre-exponential factor
R_f	Retention factor
R_s	Solution resistance
R	Substituent group
θ	Surface coverage
R	Universal gas constant

LIST OF ABBREVIATIONS

COSY	^{1}H-^{1}H correlation spectroscopy
DNS	3,5-dinitro salicylic acid
AC	Alternating current
NH_3	Ammonia
NH_4OH	Ammonium hydroxide
NH_4OH	Ammonium hydroxide
Na_2SO_4	Anhydrous sodium sulphate
$Bi(NO_3)_3$	Bismuth (III) nitrate
CRDAE	*Catharanthus roseus* dichloromethane alkaloid extract
CRDNAE	*Catharanthus roseus* dichloromethane non-alkaloid extract
CREs	*Catharanthus roseus* extracts
CRME	Catharanthus roseus methanol extract
CC	Column chromatography
Cpd	Compound
CPE	Constant phase element
CE	Counter electrode
$CDCl_3$	Deuterated chloroform
CD_3OD	Deuterated methanol
MeOD	Deuterated methanol
DM	Diabetes Mellitus
CH_2Cl_2/ DCM	Dichloromethane
DAE	Dichloromethane alkaloid extract
DNAE	Dichloromethane non-alkaloid extract
DMSO	Dimethyl sulfoxide
DMAPP	Dimethylallyl diphosphate
DEPT	Distortionless enhancement by polarisation transfer
d	Doublet
dd	Doublet of doublets
dt	Doublet of triplets
EIS	Electrochemical impedance spectroscopy
EDX	Energy dispersive X-ray

FA	Fatty acid
FAS	Fatty acid synthase
$FeCl_3$	Ferric chloride
FRAP	Ferric Reducing Antioxidant Power
FT-IR (ATR)	Fourier transformer infrared (Attenuated total reflectance)
GDP	Gross Domestic Product
HMBC	Heteronuclear multiple bond coherence
HSQC	Heteronuclear single quantum coherence
HRESIMS	High resolution electrospray ionisation mass spectroscopy
HIV	Human immunodeficiency viruses
HCl	Hydrochloric acid
OH	Hydroxy group
IE	Inhibition efficiency
IPP	Isopentenyl pyrophosphate
KTDAE	*Kopsia teoi* dichloromethane alkaloid extract
KTDNAE	*Kopsia teoi* dichloromethane non-alkaloid extract
KTEs	*Kopsia teoi* extracts
KTME	*Kopsia teoi* methanol extract
LC-TOF-MS	Liquid chromatography time-of-flight mass spectrometer
MeOH	Methanol
ME	Methanol extract
MS	Mild steel
m	Multiplet
NACE	National Association of Corrosion Engineers
NMR	Nuclear magnetic resonance
1D NMR	One-dimensional nuclear magnetic resonance
OCP	Open circuit potential
$K_3Fe(CN)_6$	Potassium hexacyanoferrate (III)
KI	Potassium iodide
PDP	Potentiodynamic polarisation
RE	Reference electrode
RCSB	Research Collaboratory for Structural Bioinformatic
SCE	Saturated calomel electrode
SFA	Saturated fatty acid

SEM	Scanning electron microscopy
STDs	Sexually transmitted diseases
s	Singlet
Na_2CO_3	Sodium carbonate
NaCl	Sodium chloride
NaOH	Sodium hydroxide
Na_2SO_4	Sodium sulphate
SD	Standard deviations
TMS	Tetramethylsilane
TLC	Thin layer chromatography
$C_2HCl_3O_2$	Trichloroacetic acid
t	Triplet
td	Triplet of doublets
2D NMR	Two-dimensional nuclear magnetic resonance
T2DM	Type 2 Diabetes Mellitus
UV	Ultraviolet
UFA	Unsaturated fatty acid
WE	Working electrode

LIST OF APPENDICES

AKTIVITI ANTI-DIABETES SEBATIAN-SEBATIAN KIMIA YANG DIPENCILKAN DARIPADA *Kopsia teoi* DAN *Catharanthus roseus* (APOCYNACEAE), SERTA KAJIAN PERENCATAN KAKISAN EKSTRAKNYA

ABSTRAK

Kajian ini melibatkan pengekstrakan kulit yang telah dikering dan dikisar daripada *Kopsia teoi* (*K. teoi*) dan *Catharanthus roseus* (*C. roseus*), menggunakan pelarut *n*-heksana, diklorometana (DCM), dan metanol (MeOH) untuk menghasilkan ekstrak mentah. Alkaloid diasingkan daripada ekstrak DCM positif Dragendorff melalui pengekstrakan asid-bes dengan HCl dan NH_4OH, menghasilkan ekstrak alkaloid DCM. Pemfaksiran menggunakan CC dan analisis dengan TLC membawa kepada pemurnian lanjut, mengasingkan alkaloid. Daripada *K. teoi*, sepuluh sebatian telah dipencilkan, termasuk empat sebatian baharu: 16-*epi*-deasetilakuammilin *N*(4)-metilena klorida (**602**), *N*(1)-metoksikarboni-11-metoksi-12-hidroksi-Δ^{14-17}-kopsinin (**603**), *N*(1)-metoksikarboni-11,12-metilenedioksi-Δ^{14-17}-kopsinin (**604**) dan *N*(4)-hidroksimetil-kopsinin **(605)**. Tambahan pula, sebatian yang telah dilaporkan turut dipencilkan, termasuklah leukonolam (**301**), kopsiloskin G **(413),** *E*-akuammidin (**132**), *N*(1)-metoksikarboni-12-metoksi-$\Delta^{16,17}$-kopsinin (**302**), kopsinat (**312**) dan *N*(1)-metoksikarboni-11,12-metilenedioksi-$\Delta^{16,17}$-kopsinin (**383**). Sementara itu, daripada *C. roseus*, lima sebatian telah dipencilkan, termasuklah satu sebatian baharu: 16-*epi*-deasetilakuammilin-7-metil-*N*(4)-metilena klorida (**606**) dan empat sebatian yang telah diketahui sebelum ini, iaitu: *β*-amirin (**590**), asid ursolik **(591**), asid dodekanoik (**596**) dan asid oleik (**598**). Sebatian-sebatian yang dipencilkan ini telah dicirikan menggunakan FT-IR (ATR), NMR 1D dan 2D, spektroskopi UV serta High

resolution electrospray ionisation mass spectroscopy (HRESIMS) dan perbandingan dengan data literatur. Sebatian-sebatian yang dipencilkan ini telah dinilai untuk aktiviti anti-hiperglisemik *in vitro* terhadap enzim *α*-amilase. Antaranya, sebatian **383** mempamerkan perencatan tertinggi dengan IC_{50} 18.3 ± 0.3 µM, diikuti oleh sebatian **604** dengan IC_{50} 18.9 ± 0.1 µM. Sebatian lain, termasuk **606**, **301**, **605**, **312**, dan **302**, menunjukkan perencatan yang kuat dengan nilai IC_{50} masing-masing 20.3 ± 0.7, 21.7 ± 1.2, 25.0 ± 0.4, 30.0 ± 0.8, dan 34.1 ± 0.1 µM, berbanding IC_{50} kawalan (akarbosa), iaitu 34.4 ± 0.1 µM. Selain itu, ujian Ferric Reducing Antioxidant Power (FRAP) telah dijalankan untuk menilai kapasiti antioksidan ekstrak, memberikan gambaran mengenai peranannya dalam aktiviti biologi dan perencatan kakisan. Kedua-dua ekstrak daripada *K. teoi* dan *C. roseus* selanjutnya diuji untuk kapasiti perencatan kakisan pada keluli lembut (MS) dalam 0.5 M HCl pada pelbagai kepekatan (10, 50, 100, 250, dan 500 ppm). Hasil spektroskopi impedans elektrokimia (EIS) dan polarisasi potensiodinamik (PD) menunjukkan peningkatan kecekapan perencatan dengan peningkatan kepekatan. Antara ekstrak yang diuji, ekstrak metanol daripada *K. teoi* dan *C. roseus* menunjukkan kecekapan perencatan tertinggi, masing-masing pada 93.51% dan 88.73%. Kedua-dua ekstrak bertindak sebagai perencat jenis campuran, seperti yang disahkan oleh analisis isoterm Langmuir. Nilai ΔG_{ads} menunjukkan kehadiran fisisorpsi dan kemisorpsi yang berkesan, dengan penjerapan spontan melibatkan interaksi fizikokimia. Peningkatan tenaga pengaktifan (Ea) dan ΔH yang positif menunjukkan proses endotermik, manakala ΔS yang negatif menunjukkan proses berasosiasi. SEM-EDX mengesahkan peningkatan rintangan kakisan melalui pembentukan lapisan pelindung di permukaan. Kesimpulannya, kajian ini telah mengasingkan dan mencirikan sebatian baharu dan yang telah diketahui daripada K. teoi dan C. roseus, yang menunjukkan aktiviti penghambatan α-

amilase, antioksidan, dan perlindungan kakisan yang ketara. Hasil ini mencadangkan potensi dwi-fungsi sebatian tersebut sebagai agen antidiabetik semula jadi dan bahan antikakisan dengan aplikasi farmakologi dan industri yang bernilai.

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ABSTRACT

This research involved extracting dried ground bark from *Kopsia teoi* (*K. teoi*) and *Catharanthus roseus* (*C. roseus*) using *n*-hexane, dichloromethane (DCM), and methanol (MeOH) solvents to produce the crude extracts. Alkaloids were isolated from Dragendorff-positive DCM extracts *via* acid-base extraction with HCl and NH_4OH, yielding a DCM alkaloid extract. Fractionation by CC and analysis by TLC led to further purification, isolating alkaloids. From *K. teoi*, ten compounds were isolated, including four new compounds: 16-*epi*-deacetylakuammiline *N*(4)-methylene chloride (**602**), *N*(1)-methoxycarbonyl-11-methoxy-12-hydroxy-Δ^{14-17}-kopsinine (**603**), *N*(1)-methoxycarbonyl-11,12-methylenedioxy-Δ^{14-17}-kopsinine (**604**), and *N*(4)-hydroxymethyl-kopsinine (**605**). Additionally, known compounds were isolated, including leuconolam (**301**), kopsiloscine G (**413**), *E*-akuammidine (**132**), *N*(1)-methoxycarbonyl-12-methoxy-$\Delta^{16,17}$-kopsinine (**302**), kopsininate (**312**), and *N*(1)-methoxycarbonyl-11,12-methylenedioxy-$\Delta^{16,17}$-kopsinine (**383**). Meanwhile, from *C. roseus*, five compounds were isolated, including one new compound: 16-*epi*-deacetylakuammiline-7-methyl-*N*(4)-methylene chloride (**606**), and four known compounds, namely: *β*-amyrin (**590**), ursolic acid (**591**), dodecanoic acid (**596**), and oleic acid (**598**). The isolated compounds were characterised using FT-IR (ATR), 1D- and 2D- NMR, UV spectroscopy, and High-resolution electrospray ionisation mass spectroscopy (HRESIMS), with comparison to literatures data. The isolated compounds were evaluated for *in vitro* anti-hyperglycaemic activity against the *α*-

amylase enzyme. Among them, compound **383** exhibited the highest inhibition with an IC_{50} of 18.3 ± 0.3 µM, followed by compound **604** with an IC_{50} of 18.9 ± 0.1 µM. Other compounds, including **606**, **301**, **605**, **312**, and **302**, showed potent inhibition with IC_{50} values of 20.3 ± 0.7, 21.7 ± 1.2, 25.0 ± 0.4, 30.0 ± 0.8, and 34.1 ± 0.1 µM, respectively, compared to the IC_{50} of the control (acarbose), which was 34.4 ± 0.1 µM. In addition, the Ferric Reducing Antioxidant Power (FRAP) assay was conducted to assess the antioxidant capacity of the extracts, providing insight into their potential role in both biological activity and corrosion inhibition. Both extracts from *K. teoi* and *C. roseus* were further subjected to corrosion inhibition capacity testing on mild steel (MS) in 0.5 M HCl at various concentrations (10, 50, 100, 250, and 500 ppm). Electrochemical impedance spectroscopy (EIS) and potentiodynamic polarisation (PD) results showed increasing inhibition efficiency with concentration. Among the extracts tested, the methanol extracts from *K. teoi* and *C. roseus* exhibited the highest inhibition efficiency, at 93.51% and 88.73%, respectively. Both extracts acted as mixed-type inhibitors, as confirmed by Langmuir isotherm analysis. The ΔG_{ads} values indicated effective physisorption and chemisorption. Spontaneous adsorption involved physicochemical interactions. Increased activation energy (Ea) and positive ΔH suggested an endothermic process, while negative ΔS indicated association. SEM-EDX confirmed enhanced corrosion resistance through the formation of a protective surface film. In conclusion, this study isolated and characterised new and known compounds from *K. teoi* and *C. roseus*, showing notable *α*-amylase inhibitory, antioxidant, and corrosion inhibition activities. These results suggest their dual potential as natural antidiabetics and anticorrosive materials with valuable pharmacological and industrial applications.

CHAPTER 1

INTRODUCTION

1.1 General introduction

Natural products play a vital role in drug discovery and development, with numerous compounds currently undergoing clinical trials (Chaachouay, & Zidane, 2024; (Domingo-Fernández et al., 2024). Natural product chemistry primarily focuses on secondary metabolites, which are non-essential metabolic products that contribute to ecological functions such as defence and reproduction (Singh et al., 2023). To date, over 2,140,000 secondary metabolites have been identified, including alkaloids, terpenoids, and phenolic compounds, which exhibit various biological and physical applications (Al-Khayri et al., 2023).

Plants, particularly higher plants, have a long-standing history in traditional medicine, with many serving as the foundation for modern pharmaceuticals. Since the early 19^{th} century, plant-derived drugs have been extensively studied, with approximately 25% of current pharmaceuticals originating from plant sources (Jabeen et al., 2014; Najmi et al., 2022). Nevertheless, only around 15% of known plant species have been systematically investigated (Lautié et al., 2020). Tropical rainforests, which host vast biodiversity, remain largely underexplored in medicinal research. Although an estimated 250,000 higher plant species exist globally, only about 12% have been screened for their medicinal potential (Cordell, 2014; Sarker & Nahar, 2007). Given that 80% of the population in developing countries relies on traditional remedies, the importance of plant-derived drugs is indisputable (Bowsher et al., 2008). Notably, the global market value of the top eight plant-derived drugs alone is estimated at USD 16 billion (Sarker & Nahar, 2007).

Malaysia is recognised as one of the 12 “megadiversity” countries, home to approximately 60% of the world’s known species. The country harbours around 15,000 species of flowering plants and over 1,170 species of ferns, with 26% of Peninsular Malaysia’s tree species being endemic (Ahmad et al., 2010). While extensive research has been conducted on tree flora, the taxonomy of non-tree species remains insufficiently explored (Tam, 1999).

Diabetes Mellitus (DM) is a rapidly growing metabolic disorder characterised by chronic hyperglycaemia, posing a major global public health challenge (Jadalla et al., 2022). In 2017, 451 million individuals worldwide were affected by diabetes, with healthcare expenditures reaching USD 850 billion. By 2045, the number of cases is projected to rise to 693 million (Cho et al., 2018; Lin et al., 2020). In Malaysia, the prevalence of diabetes increased from 11.2% in 2011 to 18.3% in 2019, ranking among the highest globally (Ganapathy, 2019). Projections indicate that by 2025, approximately 7 million Malaysian adults will have diabetes, with an estimated prevalence of 31.3% (Akhtar et al., 2022).

One strategy to manage postprandial hyperglycaemia involves the inhibition of carbohydrate metabolism (Ahmed et al., 2022). α-Amylase plays a key role in the hydrolysis of long-chain carbohydrates into smaller, absorbable molecules (Ullah et al., 2022). Persistent hyperglycaemia may lead to severe complications, including organ damage, blindness, kidney failure, heart attacks, and strokes (Gupta et al., 2020). Although synthetic inhibitors such as acarbose and voglibose are used to regulate postprandial glucose levels, they are often associated with undesirable side effects (Venkatakrishnan et al., 2019). As a result, increasing attention has been given to natural α-amylase inhibitors as safer alternatives (Golovinskaia & Wang, 2023).

Herbal remedies have been widely explored for the treatment of diabetes, with over 400 medicinal plants documented for their therapeutic potential (Samarakoon et al., 2020).

Natural products also hold significant industrial relevance, notably in the development of corrosion inhibitors aimed at producing environmentally friendly chemicals. Plant-based corrosion inhibitors are preferred due to their sustainability, accessibility, and renewability (Lemes et al., 2022). In contrast to synthetic inhibitors, which often pose environmental and health risks, plant extracts provide non-toxic, biodegradable alternatives (Al-Amiery et al., 2023).

Corrosion, the deterioration of materials due to environmental exposure, adversely impacts several industries, including transportation, infrastructure, and manufacturing. Common manifestations of corrosion include rusting, tarnishing, and discoloration (Alemayehu & Birahane, 2014). Mild steel (MS), widely used in industrial applications, is particularly vulnerable to corrosion in acidic environments, which are common in sectors such as oil well acidising, acid cleaning, and petrochemical processing. Acidic media, including hydrochloric and sulphuric acid, significantly accelerate metal degradation, thereby necessitating effective corrosion inhibitors (Hussin et al., 2016; Raja et al., 2013).

Organic compounds containing heteroatoms such as nitrogen (N), oxygen (O), sulphur (S), and phosphorus (P), along with polar functional groups and aromatic rings, are recognised as effective corrosion inhibitors. Their effectiveness stems from their ability to adsorb onto metal surfaces and form protective films (Du Plessis et al., 2022; Hsu et al., 2023). Among acid solutions, hydrochloric acid (HCl) is particularly prevalent, further emphasising the urgent need for effective and eco-friendly corrosion

inhibitors. In this context, plant-derived compounds present a promising solution for sustainable industrial applications.

In conclusion, the study of natural products remains integral to both drug discovery and industrial innovation. With the increasing global burden of diabetes, natural α-amylase inhibitors offer a promising alternative to conventional synthetic drugs. Likewise, plant-derived corrosion inhibitors provide an environmentally sustainable solution for material protection across various industries. Considering Malaysia's rich biodiversity, continued research into its native flora may lead to the discovery of novel bioactive compounds with significant medicinal and industrial potential.

1.2 Research background

Malaysia, located in the heart of Southeast Asia, is a tropical country renowned for its rich biodiversity, including over 15,000 species of flora (Keong, 2016). This vast array of plant species, supported by Malaysia's equatorial climate and abundant rainfall, has long been a focal point for researchers, particularly in the field of natural product chemistry. Medicinal plants from Malaysian forests have been a source of bioactive compounds or secondary metabolites, which are known for their significant pharmacological activities (Chan et al., 2016; Harun et al., 2015). Unlike primary metabolites, secondary metabolites do not directly affect plant growth and development (Singh et al., 2023). However, they have fascinated organic chemists since the 1850s due to their complex chemical properties and potential therapeutic applications (Croteau et al., 2000; Rosales et al., 2020). These metabolites are classified into three main groups based on their biosynthetic pathways: terpenoids,

alkaloids, and phenolic compounds, each offering unique pharmacological benefits (Sánchez & Demain, 2011).

One of the critical health challenges addressed through natural product chemistry is Diabetes Mellitus, particularly Type 2 Diabetes Mellitus (T2DM), which is prevalent globally. T2DM is characterised by insulin resistance, pancreatic β-cell dysfunction, and overproduction of hepatic glucose, leading to chronic hyperglycaemia (Bhatti et al., 2022). The inhibition of α-amylase, an enzyme responsible for carbohydrate breakdown, is a promising strategy to manage postprandial hyperglycaemia (Ogunyemi et al., 2022). By slowing the conversion of complex carbohydrates into glucose, α-amylase inhibitors can effectively reduce glucose absorption into the bloodstream (Ogunyemi et al., 2022). This study focuses on evaluating the anti-hyperglycaemic activity of compounds isolated from *K. teoi* and *C. roseus*. The inhibitory activity of these compounds was assessed through *in vitro* assays. The objective of these investigations is to identify potent α-amylase inhibitors that could contribute to the development of new therapeutic agents for diabetes management.

In addition to their pharmacological potential, *K. teoi* and *C. roseus* have also been investigated for their ability to inhibit corrosion. Corrosion, particularly in mild steel exposed to acidic environments, poses significant challenges in industries. The use of plant extracts as eco-friendly corrosion inhibitors is a promising approach to mitigate this issue. This study examines the efficacy of different extracts from *K. teoi* and *C. roseus* in preventing mild steel corrosion in hydrochloric acid solutions. Techniques such as electrochemical impedance spectroscopy (EIS) and potentiodynamic polarisation (PD) were employed to evaluate the inhibition performance, revealing that these extracts function as mixed-type inhibitors and form

protective monolayers on the steel surface. The study's findings highlight the dual potential of these plant extracts in both medicinal and industrial applications, emphasising their importance in natural product chemistry and materials science.

Moreover, the environmental and economic benefits of utilising plant-based corrosion inhibitors cannot be overstated. Traditional corrosion inhibitors often involve the use of synthetic chemicals that can be harmful to the environment and human health. In contrast, plant-derived inhibitors offer a sustainable and less toxic alternative (González-Parra & Di Turo, 2024). This research not only contributes to the understanding of how *K. teoi* and *C. roseus* extracts can protect metal surfaces from corrosion but also aligns with global efforts to promote green chemistry and sustainable industrial practices. By demonstrating the effectiveness of these natural inhibitors, the study provides a compelling case for further exploration and potential commercialisation of plant-based solutions in corrosion management. The integration of pharmacological and industrial applications in this research highlights the multifaceted benefits of natural product chemistry, paving the way for future innovations in both fields.

1.3 Problem statements

Natural products have long been a valuable source of bioactive compounds for both medicinal and industrial applications. However, many plant species remain underexplored regarding their phytochemical composition and multifunctional applications. *K. teoi* and *C. roseus* (Apocynaceae) are recognised for their medicinal properties, yet their chemical constituents have not been sufficiently characterised. Without detailed phytochemical profiling, their potential bioactive compounds cannot be fully understood or utilised for therapeutic and industrial purposes. This highlights

the need for systematic extraction, isolation, purification, and structural elucidation of their phytochemicals using advanced chromatographic and spectroscopic techniques.

This research addresses the dual challenges of managing chronic conditions such as diabetes and the degradation of industrial materials due to corrosion. Diabetes is a widespread global health issue that requires continuous exploration for more effective, safer, and natural therapeutic agents. The α-amylase enzyme plays a significant role in carbohydrate digestion, and inhibiting it is a targeted strategy for managing postprandial hyperglycaemia, a common challenge for diabetics. Natural compounds, particularly phytochemicals from plants like *Kopsia* and *Catharanthus* have shown promise in this area. However, their potential has not been fully explored. This knowledge gap emphasises the need for comprehensive research to extract, purify, and characterise these compounds in order to evaluate their efficacy as natural anti-diabetic agents.

Simultaneously, the industrial challenge of corrosion, especially the corrosion of mild steel in acidic environments poses a significant financial and operational burden across various sectors. Traditional corrosion inhibitors are often effective but come with environmental and health risks, prompting the search for greener, safer alternatives. The potential of natural plant extracts, particularly those from *Kopsia* and *Catharanthus*, as eco-friendly corrosion inhibitors represent an innovative solution that could revolutionise corrosion management practices.

Moreover, Oxidative stress plays a critical role in both diabetes progression and metal corrosion, contributing to significant health and industrial challenges. Plant-derived antioxidants can mitigate biological oxidative stress in diabetes and electrochemical oxidation in metal corrosion. However, the direct link between anti-

diabetic and anti-corrosive activities has not been extensively studied. Evaluating the antioxidant potential of these plant extracts through the Ferric Reducing Antioxidant Power (FRAP) assay will provide valuable insights into their dual applications.

Therefore, this study focuses on two primary concerns: firstly, the need for new, natural anti-diabetic agents that provide a safer alternative to current synthetic drugs by inhibiting the α-amylase enzyme, and secondly, the imperative for sustainable, effective corrosion inhibitors that can protect industrial materials without adverse environmental impacts. This study aims to bridge these gaps by leveraging the phytochemical potential of *Kopsia teoi* and *Catharanthus roseus*, thus contributing to the fields of medicinal chemistry and materials science in a manner that could have far-reaching implications for public health and industrial sustainability.

1.4 Research objectives

Research conducted for this study was based on the following objectives:

i. To extract, isolate, purify, characterise and elucidate the phytochemicals from the barks of *Kopsia teoi* and *Catharanthus roseus* (Apocynaceae) using various chromatographic and spectroscopic methods.

ii. To establish the correlation between anti-diabetic and anti-corrosive activities, the FRAP assay will evaluate the antioxidant properties.

iii. To evaluate the effect of pure compounds on the *in vitro* inhibition of the α-amylase enzyme as a measure of anti-diabetic activity.

iv. To investigate the corrosion inhibition performance of the plant crude extracts against mild steel in 0.5 M HCl media.

v. To perform SEM-EDX analysis to confirm the surface morphology and elemental composition of mild steel after corrosion inhibition treatment.

1.5 Scope of research

The study involves the separation, isolation, elucidation, and characterisation of alkaloids, triterpenoids, and fatty acids from *Kopsia teoi* and *Catharanthus roseus* using various chromatographic and spectroscopic techniques, including thin-layer chromatography (TLC), column chromatography (CC), nuclear magnetic resonance (NMR), UV-Vis spectroscopy, FT-IR (ATR) spectroscopy, and high-resolution electrospray ionisation mass spectrometry (HRESIMS). The isolated compounds were subjected to *in vitro* evaluation against the α-amylase enzyme. Additionally, the research includes the investigation of extracts from both plants as potential corrosion inhibitors for mild steel in a 0.5 M HCl medium. The corrosion inhibition efficacy was evaluated using electrochemical measurements, including electrochemical impedance spectroscopy (EIS) and potentiodynamic polarisation (PDP) analyses. Adsorption mechanisms were interpreted through Langmuir, Frumkin, and Temkin isotherms, and further supported by surface analysis using SEM-EDX techniques. Furthermore, the Ferric Reducing Antioxidant Power (FRAP) assay was performed to assess the antioxidant potential of the extracts, providing valuable insight into their potential role in both biological activity and corrosion inhibition.

CHAPTER 2

LITERATURE REVIEW

2.1 Overview

This chapter meticulously establishes the scientific foundation for investigating the potential of *K. teoi* and *C. roseus* as a source of natural products with two distinct applications: anti-hyperglycaemic activity and corrosion inhibition. Firstly, the chapter investigates the biological background of these plants. It explores their membership in the Apocynaceae family, detailing their geographical distribution, medicinal uses, and established scientific classification. This exploration highlights the potential of these plants as a source of therapeutic agents and environmentally friendly materials, given the documented medicinal applications within the Apocynaceae family. Following this broad overview, the chapter focuses on the specific chemistry of *Kopsia* and *Catharanthus*, particularly alkaloids, a diverse group of nitrogen-containing compounds known for their biological activities. Indole alkaloids, a specific subclass, are known for their therapeutic potential, and the chapter explores their presence and known properties within these two plant genera.

Broadening its scope beyond the plants themselves, the chapter lays the groundwork for the scientific concepts relevant to the research endeavours. For the investigation into anti-hyperglycaemic activity, the chapter provides a foundational understanding of diabetes and the enzymes that play a critical role in regulating blood sugar levels. This understanding is essential for designing strategies to manipulate the activity of these enzymes using natural compounds derived from plants. Similarly, in research on corrosion inhibition, this chapter explores the mechanisms by which corrosion occurs and how it can be controlled through various methods. By establishing this scientific framework, the chapter paves the way for a data-driven

investigation into the potential of *K. teoi* and *C. roseus* for both health and industrial applications.

2.2 Apocynaceae: Distribution and habitat

Apocynaceae, also known as the dogbane family, is an important family of angiosperms. It is a large and diverse group comprising approximately 5,000 species and 415 genera of trees, shrubs, woody vines, and herbs (Patil et al., 2023). The Apocynaceae family is primarily found in tropical regions, with many species inhabiting tropical rainforests. It is characterised by its flowering plants (Johan T. Venter & Verhoeven, 2001). Under the unified classification system, the Apocynaceae family has been expanded to include five subfamilies: Rauvolfioideae, Apocynoideae, Periplocoideae, Secamonoideae, and Asclepiadoideae. (Patil et al., 2023). This expansion reflects the family's significant diversity and complexity. Notably, Apocynaceae is recognised as the tenth largest angiosperm plant family (Barny et al., 2021).

Characteristic features of the Apocynaceae family include the production of white latex or occasionally watery juice by almost all species. Leaves are arranged in an opposite or whorled pattern, while flowers are characterised by their large size, vibrant colours, and subtle fragrance, featuring five contorted lobes. Fruits are typically found in pairs (Christophe & Pharm, 2006). *Kopsia* and *Catharanthus* are two notable genera within the Apocynaceae family (Chan et al., 2016). Apocynaceae species are widespread in the regions of Asia, Africa, and Latin America, mostly in tropical and subtropical regions, as well as temperate areas (Rehman et al., 2020). A majority of species within this family are toxic, while numerous others are employed medicinally owing to the presence of cardiac glycosides and a diverse array of

alkaloids (Bhadane et al., 2018; Islam & Lucky, 2019). In Malaysia, nearly 110 species classified into 34 genera of this family are distributed mostly in Peninsular Malaysia. Only 10 genera and 38 species are trees or shrubs, with the remaining being climbers or scrambling shrubs, except for *Vallariopsis lancifolia* which is an epiphytic shrub (Kartini, 2009). The only common large trees in Malaya are pulai (*Alstonia*) and jelutong (*Dyera*). The family is also well-known for its showy garden plants, many of which have been introduced and widely cultivated in Malaya, such as frangipanni (*Plumeria*) (Kartini, 2009).

Most Apocynaceae species are pollinated by insects, including butterflies, moths, bees, wasps, beetles, flies, and even cockroaches (Xiong et al., 2020), with very rare instances of bird pollination (Pauw, 1998). Interestingly, approximately 20% of the species studied thus far are considered insect generalists, meaning they are pollinated by more than three of the seven major classes of insects mentioned above. This diversity in pollinators suggests that the complexity of floral structures in Apocynaceae is not necessarily linked to a specialisation in pollinators (Ollerton et al., 2017). This broad range of pollination strategies contributes to the family's ecological success and adaptability across various environments.

2.2.1 Apocynaceae uses

Plants from the Apocynaceae family are renowned for their rich content of bioactive compounds, including alkaloids, terpenoids, steroids, flavonoids, glycosides, simple phenols, lactones, and hydrocarbons. Some members of the Apocynaceae family are widely used as ethnomedicines across the globe. Various species within the Apocynaceae family exhibit a wide range of bioactivities, including the treatment of chest complaints, neoplastic diseases, throat infections, human immunodeficiency viruses (HIV), hypertensive heart disease, sexually transmitted diseases (STDs), liver

diseases, fungal diseases, antioxidant activity, anti-inflammatory/analgesic activity, anticancer/cytotoxic activity, antimicrobial activity, cardioprotective activity, anticonvulsant activity, antimalarial activity, gastroprotective properties, relief from coughing, throat and mouth problems, fever, measles, wound healing, pain treatment, diabetes, as well as the treatment of skin infections (Figure 2.1) (Anand et al., 2020; Ekalu et al., 2019; Pereira et al., 2015). Apocynaceae species find widespread applications across various industries, including cosmetic, flavouring, food, pesticide, and pharmaceutical industries, as well as in horticulture (Aremu et al., 2011; Patil et al., 2023). Many species are extensively cultivated as ornamentals due to their beautiful flowers, and some are grown as food sources for butterflies (Joselin et al., 2012).

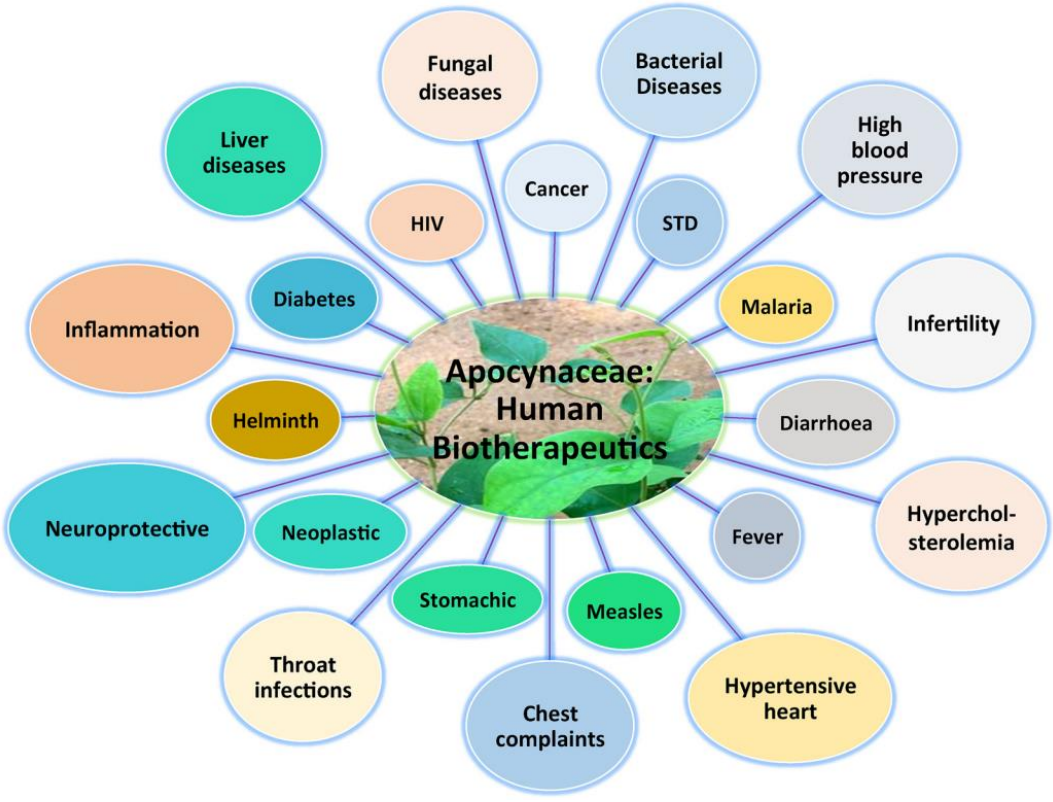


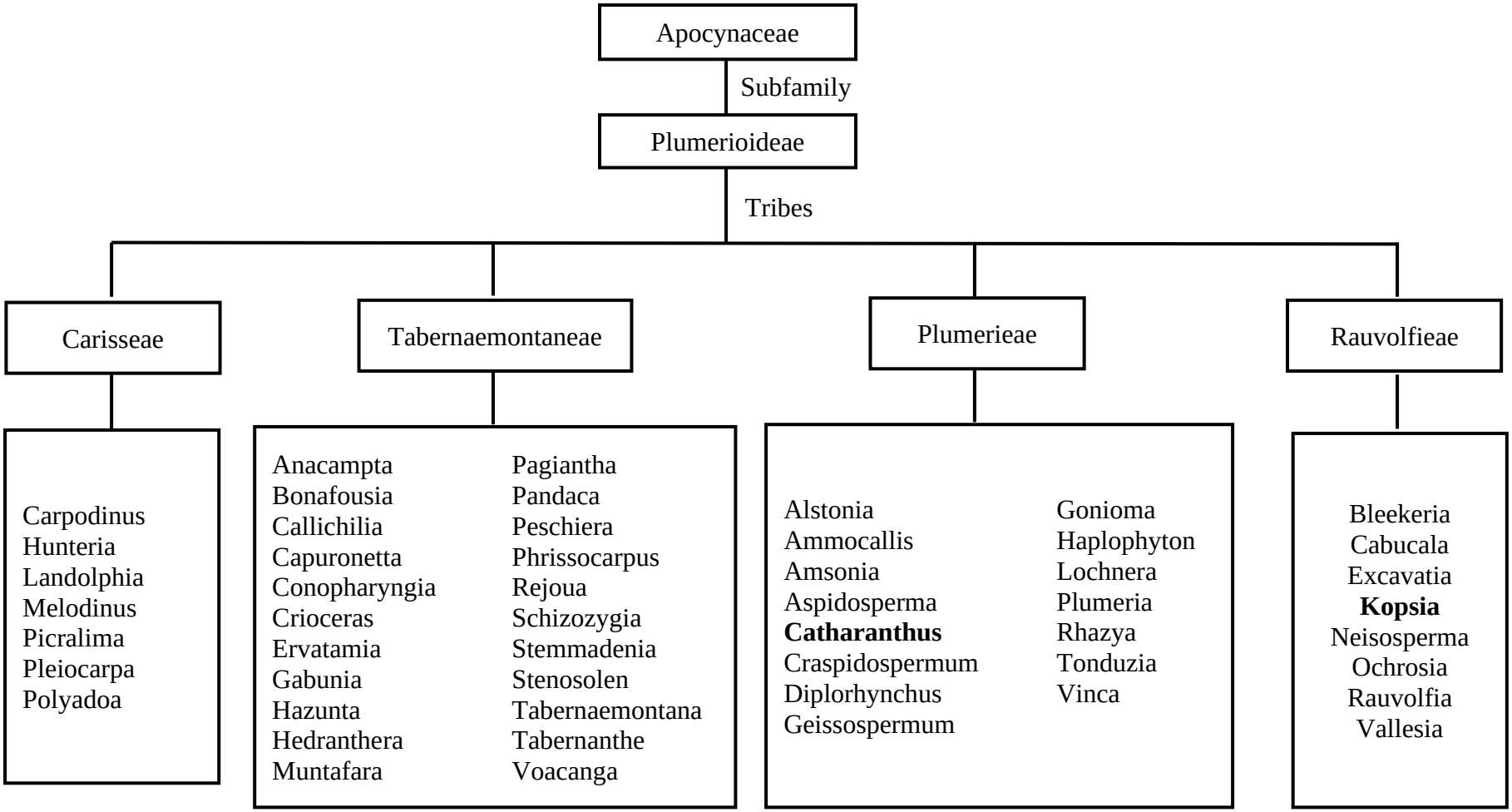
Figure 2.1 Diagrammatic illustration of Apocynaceae as potential human biopharmaceutical in the management of diseases (Anand et al., 2020).

Moreover, Apocynaceae plants are utilised in various industries beyond medicine and horticulture. Latex obtained from species such as *Hevea brasiliensis* (rubber tree) and *Landolphia* (P. Beauv.) serves as a primary source of natural rubber, supporting industries ranging from automotive to healthcare (M de Almeida, 2015). Fibres extracted from Apocynaceae species like *Wrightia tinctoria* are used in manufacturing ropes, cords, and fabrics (Ramachandran et al., 2022). Moreover, the seeds of certain Apocynaceae plants, such as *Calotropis procera*, are rich in oil, presenting a potential feedstock for biodiesel production (Al-Rowaily et al., 2020).

Furthermore, the Apocynaceae family has also emerged as a significant source of natural corrosion inhibitors, drawing considerable interest from the scientific community. The family is rich in secondary metabolites capable of forming protective films on metal surfaces, mitigating electrochemical processes responsible for corrosion (Rosli et al., 2023). These plant-based inhibitors offer effective corrosion protection while aligning with environmental sustainability goals by reducing the chemical footprint associated with metal preservation techniques (Ayilara et al., 2023; Khan et al., 2023). Additionally, the exploration of Apocynaceae plants in corrosion inhibition reflects a growing trend towards leveraging natural resources for industrial applications, offering a promising avenue for developing greener, more sustainable corrosion prevention strategies. This multifaceted utility of Apocynaceae plants emphasises their importance not only in traditional and modern medicine but also in various industrial applications, contributing to sustainable development across multiple sectors.

2.2.2 Apocynaceae classification

According to a chemotaxonomic investigation of plant families (Kisakurek et al., 1983), the Apocynaceae family is divided into several subfamilies, including the Plumerioideae subfamily. This subfamily is further divided into various tribes **(**Scheme 2.1**)**. Each tribe comprises multiple genera. *Kopsia* and *Catharanthus* are classified as members of distinct tribes within the Apocynaceae family. *Kopsia* belongs to the Rauvolfieae tribe, whereas *Catharanthus* is a member of the Plumerieae tribe (Kisakurek et al., 1983).



Scheme 2.1 Apocynaceae family classification (Mehran, 2014).

2.3 The Genus *Kopsia*

2.3.1 Botany and distribution

Plants of the genus *Kopsia*, belonging to the Apocynaceae family, are distributed from southern China and Burma to northern Australia and Vanuatu (Middleton, 2004). However, the genus exhibits its greatest diversity in Peninsular Malaysia and Sarawak (Malaysian Borneo) (Middleton, 2004). The genus was first published in 1823 by Blume in honour of the Dutch botanist J. Kops, with one species, *K. arborea* (Middleton, 2004).

According to the most recent revision of this genus by Middleton, there are a total of twenty-four *Kopsia* species, with about eighteen species found in Malaysia, as listed in Table 2.1 along with their distribution (Middleton, 2004, 2005). The genus *Kopsia* is renowned for its rich composition of indole alkaloids. Malaysian representatives of this genus, in particular, serve as a prolific source of novel alkaloids characterised by unique or intriguing carbon skeletons and promising biological activities (Middleton, 2004; Sévenet et al., 1994).

Table 2.1 *Kopsia* species and its location in Peninsular Malaysia and Borneo (Sévenet et al., 1994).

No.	Species	Location
i	*K. arborea* Blume	Perak
ii	*K. dasyrachis* Ridl.	Sabah (Lukan)
iii	*K. deverrei* L. Allorge	Johor (Mersing)
iv	*K. fruticosa* (Roxb.) A. DC.	Sarawak
v	*K. grandifolia* D. J. Middleton	Johor (Sungai Mupar)
vi	*K. griffithii* King & Gamble var. *griffithii*	Melaka, Selangor
vii	*K. griffithii* King & Gamble var. *pubescens* D. J. Middleton	Johor (Sungai Hula Sembrong)
viii	*K. larutensis* King & Gamble	Perak
ix	*K. macrophylla* Hook. F.	Negeri Sembilan, Johor (Gunung Angsi)
x	*K. pauciflora* Hook. F. var. *pauciflora*	Melaka
xi	*K. pauciflora* Hook. F. var. *mitrephora* (Sleesen) D. J. Middleton	Sabah (Lahad Datu District)
xii	*K. profunda* Markgr.	Terengganu (Belara Forest Reserve)
xiii	*K. rajangensis* D. J. Middleton	Sarawak (Kapit)
xiv	*K.* terengganesis L. Allorge & Wiart	Terengganu (Dungun)
xv	*K. singapurensis* Ridl.	Johor (Mersing)
xvi	*K. sleeseniana* Markgr.	Sarawak (Bintulu)
xvii	*K. tenuis* Leenh. & Steenis	Sarawak (Matang)
xviii	*K. teoi* L. Allorge	Johor (Keluang)

2.3.2 General appearance and morphology

Kopsia (Apocynaceae) is a genus of evergreen shrubs and trees, occurring in lowland forests. They are characterised by their milky sap, simple opposite leaves, and terminal or axillary inflorescences. Twigs exhibit a cylindrical morphology with light brown bark characterised by longitudinal striations. Young shoots are green and

flattened at the apex. Leaves are elliptical in shape and arranged in an opposite pattern, each possessing a gland at the tip of the acumen on the dorsal side. All species are distinguished by a small to large gland located just below the sepal apex. A distinctive feature of most species within this genus is the nose-like ventral appendage of the mericarp, a cavity that is entirely separated from the seed-bearing region by a wall (Markgraf, 1972; Middleton, 2004; Sévenet et al., 1994). The flowers of *Kopsia* species are notable for their vivid colours, often presenting in shades of pink, white, or blue, with a corolla that is typically tubular or funnel-shaped, leading to a distinctive appearance that aids in pollination. The fruit of the *Kopsia* plant is a drupe, which contains numerous seeds, each encased in a hard endocarp, facilitating the spread of seeds by various dispersal agents including wind and fauna (Johns, 1995). An example of a species in this genus is *Kopsia teoi* L. Allorge, as shown in Figure 2.2 (**a**).

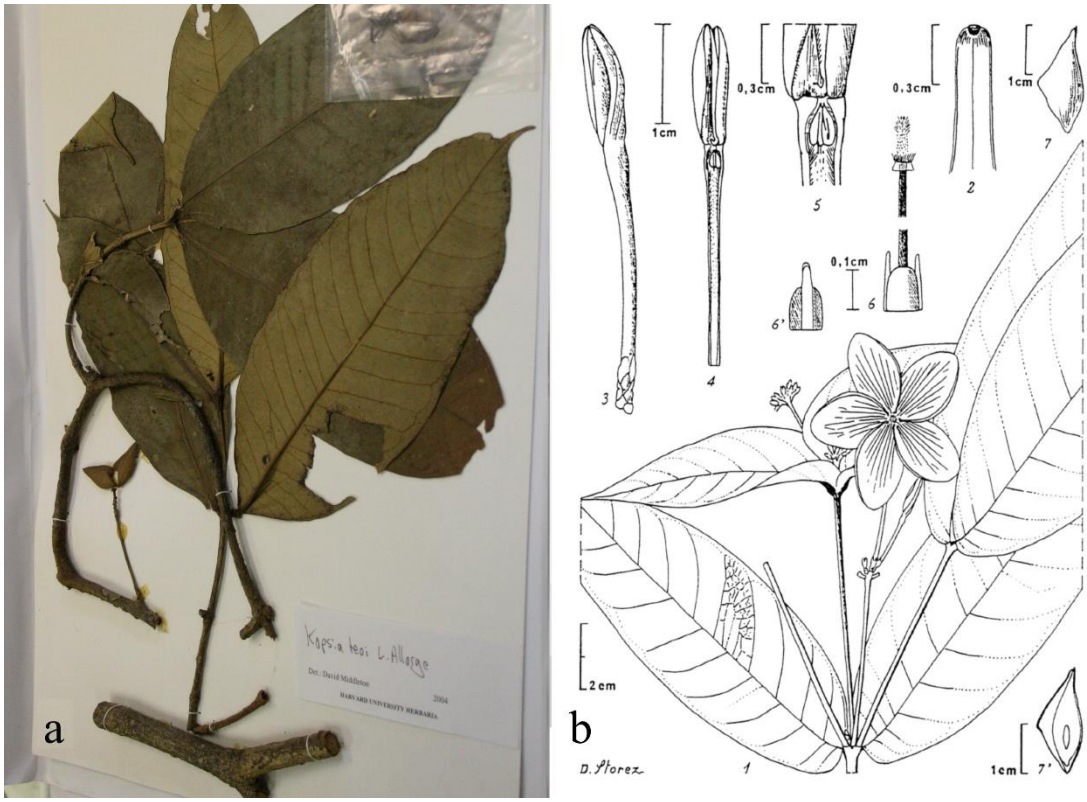


Figure 2.2 *Kopsia teoi* L. Allorge: (**a**) Herbarium catalogue specimens (Allorge, 1993), and (**b**) The illustrations of its parts (Sévenet et al., 1994).

2.3.3 Medicinal uses

Many *Kopsia* species are rich in secondary metabolites, such as monoterpenes and indole alkaloids, which are renowned for their therapeutic benefits. These compounds have been extensively identified for their medicinal properties. The presence of these bioactive compounds highlights the potential importance of *Kopsia* species in traditional medicine and modern pharmacological research. For instance, in Chinese folk medicine, *K. officinalis* is utilised to alleviate rheumatoid arthritis, pharyngitis, tonsillitis, and dropsy (Hop & Son, 2022). Similarly, in Malaysia, the roots of species like *K. larutensis*, *K. macrophylla*, *K. singapurensis*, and *K. paucifora* are traditionally used as a poultice for treating ulcerated noses in cases of tertiary syphilis (Hop & Son, 2022). These traditional uses highlight the plant's rich history in medicinal practices and its potential for treating various ailments (Jin et al., 2022; Kadereit & Bittrich, 2019).

Further research into the pharmacological effects of *Kopsia* constituents has revealed a broad spectrum of therapeutic potentials, including anticancer, anti-manic, antimicrobial, anti-inflammatory, anti-allergic, anti-diabetic, anti-tussive, antinociceptive, acetylcholinesterase (AChE) inhibitory, cardiovascular, and vasorelaxant activities, especially cytotoxicity (Hop & Son, 2022). These findings emphasis the significance of *Kopsia* species in the field of pharmacological discoveries, offering promising avenues for the development of novel treatments for infections, inflammation, allergies, diabetes, and cancer (Chen et al., 2011, 2014; Hop & Son, 2022). The ongoing exploration of *Kopsia* plants as a reservoir of novel and bioactive compounds continues to contribute valuable insights into their extensive medicinal uses and benefits.

2.3.4 *Kopsia teoi*

Kopsia teoi L. Alorge is grown in Peninsular Malaysia. It was found in the lowland of evergreen forests from 200 m altitude (Middleton, 2004). This species characteristically grows as a tree reaching 4 meters in height, with smooth branchlets and elliptical leaves ranging from 6 to 22 cm in length and 2.1 to 9.2 cm in width, with a pointed apex and rounded to acute base. The secondary veins, numbering 11 to 15 pairs, are prominent and spaced 5 to 18 mm apart, diverging at angles of 50 to 70 degrees from the midrib. The inflorescence is dichasial, measuring 5.6 to 6.3 cm in length, with glabrous branches and peduncles. The corolla is predominantly white with pink accents or entirely pink, exhibiting a tube 34 to 41 mm long and 2.7 to 2.8 mm wide, significantly longer than the lobes and calyx. Stamens are positioned approximately 35.0 to 37.5 mm from the base of the corolla tube, bearing anthers measuring 1.7 to 1.9 mm in length and 0.5 mm in width, with filaments measuring 0.9 to 1.4 mm. The disk is roughly 1.2 mm long, slightly surpassing the ovaries, while the style measures 34.0 to 37.5 mm, with a style head measuring 0.9 to 1.1 mm. The complete fruit description remains unidentified. However, it is known that the fruit consists of 1 or 2 triangular mericarps, dilated near the middle, as shown in Figure 2.2 (**b**) (Allorge, 1993; Middleton, 2004).

2.4 The genus Catharanthus

2.4.1 Botany and distribution

Among the family Apocynaceae, *Catharanthus* belongs to the subtribe Catharanthinae of the tribe Plumerieae, subfamily Plumeroideae. This genus comprises eight species: *Catharanthus roseus*, *Catharanthus trichophyllus*, *Catharanthus lanceus*, *Catharanthus ovalis*, *Catharanthus longifolius*, *Catharanthus*

scitulus, Catharanthus coriaceus and *Catharanthus pusillus* (Leeuwenberg, 1994; Van Bergen, 1996), distributed across various tropical and subtropical regions of the world. The botanical characteristics of *Catharanthus* include glossy, green leaves and flowers that range in colour from white to pink, with a distinctive reddish centre. These plants have adapted to a variety of environmental conditions, from the dry, subtropical forests of Madagascar to humid, tropical climates. The botany and taxonomy of the *Catharanthus* genus have been extensively studied, revealing a complex interplay between the species' morphological traits and their ecological niches, which has facilitated their widespread cultivation and naturalisation beyond their native habitat (Johnson et al., 1963; Van Der Heijden et al., 2004).

Although endemic to Madagascar, human cultivation and naturalisation efforts have expanded the presence of *Catharanthus* species to many tropical and subtropical regions worldwide, including parts of Asia, Africa, and the Americas. In this genus, seven species are endemic to Madagascar, while one species, *C. pusillus*, is endemic to India. Some species have a limited distribution in Madagascar, each with its own central location. *C. trichophyllus* is found in the northwestern region, while *C. lanceus* is typically found near Antananarivo. *C. coriaceus* can be seen near the Itremo Mountains, and *C. ovalis* is commonly found around Parc Isalo. In addition, *C. longifolius* is typically found near Ambalavao, while *C. scitulus* can be found in the south-central area of the country. As for *C. roseus*, it is believed to originate from the Fort Dauphin area in the southeasternmost part of Madagascar but has also been cultivated as an ornamental plant in many tropical and subtropical regions (Hickey & King, 1988; Nejat et al., 2015; Van Bergen, 1996).

2.4.2 General appearance and morphology

The *Catharanthus* genus, commonly referred to as periwinkle, comprises annual or perennial herbs or subshrubs, which frequently contain white latex and woody at the base, presenting a distinct appearance and morphology within the botanical world. Typically, these perennial herbs are characterised by their glossy, dark green leaves that grow oppositely along the stems. These leaves are elliptical to oblong in shape, featuring smooth margins. The stems of *Catharanthus* species tend to be slender and wiry, occasionally branching as the plant matures. One of the most captivating aspects of *Catharanthus* lies in its flowers, which are solitary and terminal, emerging from the leaf axils. The flowers showcase a spectrum of colours ranging from pristine white and soft pink to vibrant lavender and deep purple, contributing to the plant's ornamental appeal. Each flower consists of a five-petaled corolla with a prominent centre containing the reproductive organs. Moreover, *Catharanthus* plants produce distinctive fruit capsules housing numerous small seeds (Kulkarni et al., 2016; Naeem et al., 2017; Van Bergen, 1996).

2.4.3 Medicinal uses

All species of the genus *Catharanthus* are known for their distinctive medicinal properties, with *Catharanthus roseus* (Madagascar periwinkle) being the most studied. This genus is celebrated in the pharmaceutical world mainly for its production of two pivotal alkaloids: vincristine (**1**) and vinblastine (**2**), which have dramatically changed the landscape of chemotherapy (Figure 2.3). These compounds are utilised in the treatment of various cancers, with vincristine (**1**) being instrumental in managing childhood leukemia and vinblastine (**2**) being used against Hodgkin's disease and other cancers. The significant impact of these alkaloids stems from their ability to inhibit

mitotic cell division, which is crucial for the proliferation of cancer cells (Noble, 1990).

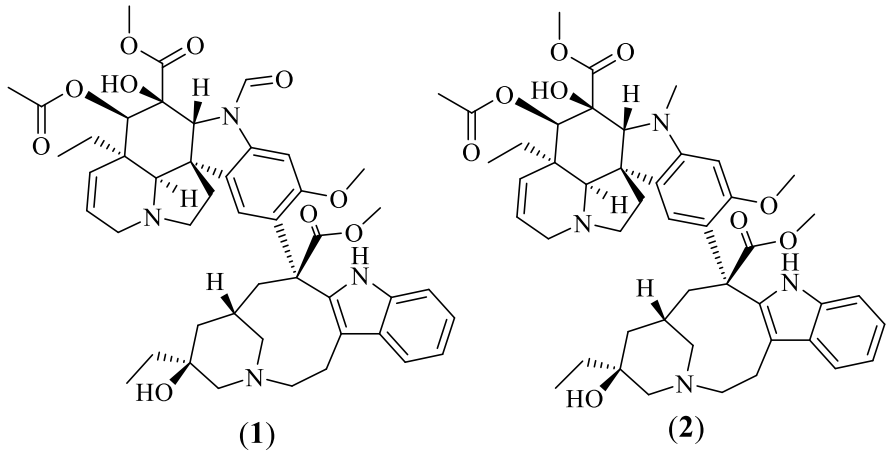


Figure 2.3 Examples of two alkaloids used in chemotherapy treatments for cancer isolated from *Catharanthus roseus*: Vincristine (**1**) and Vinblastine (**2**).

Beyond their notable anticancer activities, *Catharanthus* species have been explored for other medicinal benefits. The plants in this genus have been reported to exhibit antihypertensive, antioxidant, antifungal (Pham et al., 2020), antiplasmodial activity in human erythrocytes (Ponarulselvam et al., 2012), antidiabetic (De Vos et al., 2023), antimicrobial (Sasikumar et al., 2024), and anti-inflammatory (Borah et al., 2024) properties, attributed to their complex mixture of alkaloids and other phytochemicals (Atanasov et al., 2015). For example, some alkaloids from these plants have been investigated for their potential to manage blood sugar levels, offering a complementary approach to traditional diabetes treatment (Nammi et al., 2003; Tiong et al., 2015). Moreover, the antimicrobial properties of certain compounds in *Catharanthus* species suggest their potential utility in combating bacterial and fungal infections. The broad spectrum of biological activities exhibited by compounds derived from *Catharanthus* accentuates the genus's importance in traditional and