REVIEW ARTICLE

A Review on Pharmacological Properties of *Christia vespertilionis*

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ABSTRACT

Commonly referred to as 'daun rerama', *Christia vespertilionis* has increased in popularity in traditional and modern medicine. This review aims to report the relevance of this plant in terms of its traditional uses, pharmacological actions, phytoconstituents, extractions methods, and identify the research gaps and future potentials. The review is conducted as per PRISMA guidelines; a database search was conducted in Web of Science, Science Direct, Scopus and Google Scholar from 1996 to 2021. Results show that to date, phytochemicals such as alkaloids, flavonoids, quinones, and others have been identified, corresponding to its range of pharmacological activities that include anti-cancer, anti-malaria, and antioxidant. There have also been claims of antidiabetic activity but not supported by enough scientific evidence. Study on molecular and gene expression was still lacking. There is a good future in the research of this plant with many potential aspects to be investigated.
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Keywords: *Christia vespertilionis*, Red butterfly wing, Daun rerama, Antioxidant

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INTRODUCTION

Herbs have been a necessity since the start of humankind. Various uses have been found, but the most prominent would be herbal medicine. The earliest documented use of herbs was in the Vedas in about 4500 to 6000 BCE (1).

A herb known locally in Malaysia as the butterfly wing, because it resembles a butterfly in flight, is scientifically known as *Christia vespertilionis*. In Malay, it is known as 'daun rerama' (2,3). Native to southeast Asia, this plant is traditionally used as herbal medicine for anti-cancer and anti-malarial treatment (4–7). Some researchers have also explored the possibility for anti-inflammatory properties (8). This plant is included on Malaysia's red list of endangered species (least concern) by the International Union for Conservation of Nature and Natural Resources (IUCN).

The butterfly wing plant is commonly cultivated as an ornamental plant due to its vibrant features and unique shape (9). Some researchers have found ways to cultivate the seeds by using methods such as surface sterilisation. The surface sterilisation method could remove contaminants such as fungi and bacteria from the seeds. In Northeast Cambodia, the Bunong people in the Mondulkiri province used *C. vespertilionis* in various ways, most notably by crushing the plant with water and applying it as topical medicine (8). Over the years, many researchers have explored the pharmacological properties of this plant and conducted in vitro and in vivo experiments to discover its potential in modern medicine. This article aims to review the studies that have been conducted on *C. vespertilionis* and assess its potential phytomedicine use.

METHOD

Search Strategy

A survey was conducted using a literature search covering publications published over 25 years (1996–2021). Four databases were chosen for the literature search utilising a search string entered in the advanced search option of each database. The databases chosen were Scopus, Web of Science, Science Direct and Google Scholar. Following refinement and initial evaluation of the obtained results, we formulated a set search string:

Scopus: TITLE-ABS-KEY ("Mariposa *Christia vespertilionis*" OR "*Christia vespertilionis*" OR "red butterfly wing" OR "rerama leaf" OR "pokok rerama" OR "daun rerama").

Web of Science: TS = ("Mariposa *Christia vespertilionis*"

OR "*Christia vespertilionis*" OR "red butterfly wing" OR "rerama leaf" OR "pokok rerama" OR "daun rerama").

ScienceDirect: "Mariposa *Christia vespertilionis*" OR "*Christia vespertilionis*" OR "red butterfly wing" OR "rerama leaf" OR "pokok rerama" OR "butterfly leaf" OR "rerama" OR "daun rerama".

Google Scholar: "Mariposa *Christia vespertilionis*" OR "*Christia vespertilionis*" OR "red butterfly wing" OR "rerama leaf" OR "pokok rerama" OR "butterfly leaf" OR "rerama" OR "daun rerama".

The generalised theme of the search string aims to find all possible publications of *C. vespertilionis* to date, regardless of theme and type of publication. No confinements were set so as to maximise the findings.

Study Selection

The following criteria were used to select the studies: articles pertaining to the history of *C. vespertilionis*, the pharmacological actions of *C. vespertilionis* extracts, reports of phytochemistry or isolation of *C. vespertilionis* secondary metabolites, phytomedicinal properties of *C. vespertilionis*, or books describing traditional uses of *C. vespertilionis* and publications to be published in English or Malay. Case reports, review papers, letters to the editor and conference proceedings were included. The selected publications were examined manually to identify and exclude works that did not satisfy the previously stated criteria.

Data Extraction

The year of publication, the country where the research was done, the portion of the plant used, isolated and identified chemicals, and evaluated biological activity were all examined further in the selected articles. The experimental model, the extract and dosage used, and the results were gathered to determine the pharmacological effects. Tables and figures were created using the gathered data.

RESULTS

With the screening of each database completed, a total of 74 articles were found: 25 from Scopus, 10 from Web of Science, 9 from Science Direct and 30 from Google Scholar. For articles that were indexed in more than one database, these articles were removed to avoid duplication, which resulted of 52 articles. Subsequently, thorough inspection of inclusion and exclusion of the study, a final total of 39 articles were chosen to be included. The procedure of identification and screening is showed in Fig. 1.

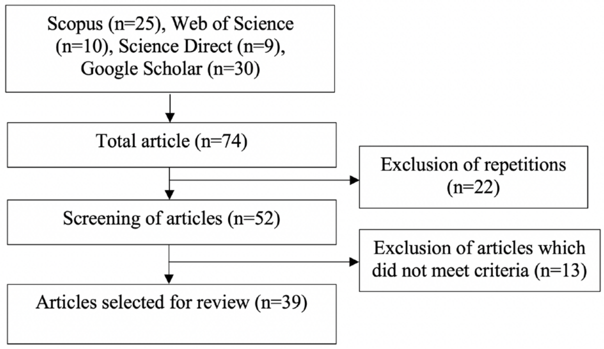

Figure 1: Flowchart for the process of identification and screening

DISCUSSION

History and Traditional Uses

C. vespertilionis plant is a well-known herbal medicine in the South Asia region. The plant is usually boiled, or some parts are chopped and soaked in water to create a paste. The resulting paste is then applied locally in injuries such as wounds and sprains, or in case of gastrointestinal disorders, the paste is eaten (10). A study showed that the *C. vespertilionis* plant may exhibit anti-inflammatory properties (7). Furthermore, *C. vespertilionis* was claimed to cure colds, muscle weakness, tuberculosis, and bronchitis (11).

The entire plant has traditionally been used to cure snake bites and tuberculosis, and the leaves are frequently applied topically to treat bone fractures. Tonsillitis, muscular weakness, colds and poor blood circulation are additional illnesses for which *C. vespertilionis* leaves have been reported to be effective (2). It is common for people to boil the leaves of *C. vespertilionis* and consume them in the form of tea.

Geographical Distribution

The earliest report of *C. vespertilionis* was described by Barham (13). In 1774, the plant was first collected by Joao de Loureiro in Conchinchina, which is now a part of Vietnam. Initially cultivated in botanic gardens as an ornamental plant, *C. vespertilionis* was also native to other parts of Asia, such as Thailand and Indochina. Nowadays, it is reported to be commonly found in several parts of Southeast Asia countries such as Vietnam, Thailand, Cambodia, Myanmar, Malaysia, and Indonesia (3,14,15). The botanical classification and description of this plant are shown in Table I.

Pharmacological Report

The pharmacological action of *C. vespertilionis* has been reported in both in vivo and in vitro studies. The majority of publications regarding *C. vespertilionis*

Table I: Botanical classification and plant description of *C. vespertilionis*

Botanical Classification			Reference
Family:Fabaceae Genus: *Christia* Species: *C. vespertilionis*			(13,16–18)

S. No.	Part of plant	Description	
1	Root	▪ Dark, yellow in colour ▪ Branched, cylindrical with ridges, furrows, and small lateral root hairs	(16)
2	Stems	▪ Hairy, cylindrical, and green in colour ▪ Herbaceous, unbranched with clear distinction of nodes and internodes	(16)
3	Leaves	▪ Trifoliate with long petiole and stipulate ▪ Exhibits alternate phyllotaxy ▪ Hairy in nature with prominent mid rib ▪ 2-4 inches wide	(11,16)

have reported it having anti-cancer, anti-malarial and antioxidant activities. Although a few animals and human cell lines have been used to evaluate anti-cancer and anti-malarial activities, the commonly used methods are chemical-based for antioxidants. Beside the three pharmacological activities mentioned, some research has also revealed the anti-inflammatory and antidiabetic activity of the plant. The various activities mention can be found in Table II.

Anti-cancer activity

In an in vitro study, the extract from *C. vespertilionis* showed inhibition for cancer cells but did not affect normal human fibroblasts (19). The antitumor activity from the *C. vespertilionis* plant is first reported by the ethyl acetate fraction CV-45, which had strong antiproliferative and proapoptotic effects in MTC-SK and KRJ-I cells. MTC-SK derived from a human medullary thyroid carcinoma while KRJ-I derived from a human carcinoid of the small intestine. It was also discovered that the gene expression of MTDH, PDCD5 and TNFRSF10b in MTC-SK and KRJ-I cells after treatment with CV-45 was altered. The genes examined have been implicated in programmed cell death. From this study, it was concluded that there are potential clinical effects for patients with neuroendocrine tumours.

Another study discovered that the methanolic extracts of *C. vespertilionis* exerted a moderate cytotoxic effect on the breast cancer cell line, MDA-MB-231, and the cytotoxicity was significantly higher than that obtained on a non-malignant cell line, NIH/3T3 (20). This finding is useful for future research to prove *C. vespertilionis* as an anti-cancer drug as it gives a more significant effect on cancerous cells than noncancerous cells. The effects caused by *C. vespertilionis* methanolic extract were also reported to be selective, as it did not have a significant effect on MCF-7, probably due to the presence of oestrogen receptor on the cell that facilitates the cell growth and hampers the induction of cell death (20).

Significant cytotoxic effects on breast cancer cell lines, particularly MDA-MB-231, a triple-negative breast cancer cell line was reported using the ethyl acetate root extract of *C. vespertilionis* (9,21). Furthermore, it has strong antioxidant properties due to its high phenolic content. Ostensibly, the study shed new light on C. vespertilionis' potential as an anti-breast cancer agent.

Beside using the extract of *C. vespertilionis* for treatment alone, there is also a possibility to combine the extract with a known chemotherapy drug to increase the cytotoxicity against cancerous cells. In a study, ethanolic extract of *C. vespertilionis* leaves exerted low cytotoxicity against all cell lines (IC50 > 1mg/mL). However, by combining *C. vespertilionis* ethanolic extract and a standard chemotherapy drug, cyclophosphamide, at a concentration of IC15 and IC25, the treatment against breast cancer cell line resulted in a synergism (CI < 1) (22).

A study stated that the extract of the *C. vespertilionis* plant leaves exhibits significant activity on Hela and MRC54 cells, inhibits the tumour cells growth of H22 and S180 and the activity of the neuroendocrine tumours (12).

Anti-malarial activity

Novel chemical compounds in *C. vespertilionis* were found to have significant antiplasmodial activity after an in vitro experiment (23). The compounds identified were christene and christanoate. The first compound, christene, was discovered to have anti-malarial action (IC50 = 9.0g/ml) against Plasmodium falciparum. This study was further strengthened with the findings from Yasin et al. (2020), where they determined that the methanolic extracts of *C. vespertilionis* leave exhibit anti-malarial activity against P. falciparum strain (20).

Cyclohexane extracts of *C. vespertilionis* were also shown to have antiplasmodial action, with IC50 values ranging from 10 to 20 g/ml. However, it is also essential to know that this compound showed high cytotoxicity upon mammalian cells (SI < 2) (8).

Anti-inflammatory activity

A study discovered the compound linoleate in the extract of *C. vespertilionis* (red leave) after analysis using LC-MS (24). Linoleate is a polyunsaturated omega-6 fatty acid ester that has anti-inflammatory, acne-reducing, and moisture-retaining effects when applied topically to the skin. Previous studies indicated that linoleate possesses anti-inflammatory activities. The anti-inflammatory properties of ethyl linoleate from A. sativum has been demonstrated to inhibit LPS-induced iNOS and COX-2

Table II: Pharmacological actions of *C. vespertilionis*

Activity	Animal, Dose, Duration, Route of Administration	Extract	Part	Model	Evaluating Parameters	Major Findings	Reference
Anticancer	In vitro	Chloroform, Ethyl acetate	Leaf, Root	Human breast carcinoma cell lines (MCF-7 and MDA-MB-231)	Cytotoxicity determined using MTT assay	Ethyl acetate root fraction F3 exhibited the most significant cytotoxic effect against breast cancer cells MCF-7 and MDA-MB-231 but showed no cytotoxic effect against 3T3 cell line.	(9)
	In vitro	Methanol	Leaf	Human breast carcinoma cell lines (MCF-7 and MDA-MB-231) and normal cell NIH/3T3	Cytotoxicity determined using MTT assay	Methanolic extract of *C. vespertilionis* reduced cell viability in MDA-MB-231 cell line but no toxic effect against MCF-7 cell line and normal cell line NIH/3T3.	(20)
	In vitro	Ethyl acetate	Aerial parts	Human medullary thyroid carcinoma (MTC), human small intestinal neuroendocrine tumour (SI-NET)	Proliferation and viability of cells analysis by cell counting and WST-1 assay, gene expression study of the apoptosis-related gene	Extracts of *C. vespertilionis* showed antiproliferative and proapoptopic effects in all MTC and SI-NET cells, especially ethyl acetate extract which showed the highest growth inhibition for MTC and SI-NET cells but not in normal human fibroblasts.	(4)
	In vitro	Ethanol	Leaf	Fibroblast (CRL2522), keratinocyte (HaCaT), liver carcinoma (HepG2), breast cancer (MCF-7), normal liver (WRL68) cell lines	Synergistic interaction between C. vespertilionis leaf extract with chemotherapy drug, cyclophosphamide via in vitro cytotoxic assay	Combination of ethanolic extract and cyclophosphamide at concentration of IC15 and IC25 resulted in synergism with CI<1.	(22)
	In vitro	Water, methanol	Whole plant	Breast cancer (MCF-7), ovarian cancer (SKOV-3), colorectal cancer (HT-29) cell line	Cytotoxicity determined through MTT assay	*Christia sp.* water extract showed better anti-proliferative effects as compared to the methanolic extract, however treatment is dose dependent.	(32)
Antimalaria	In vitro	Cyclohexane	W	*Plasmodium falciparum* NF-54 strain	Cytotoxicity assay	Cyclohexane extract of *C. vespertilionis* exhibited anti-malarial activity with IC_{50} of 10.8±1.1ug/mL.	(8)
	In vitro	Aqueous-methanol, Methanol	Stem, Leaf	*Plasmodium falciparum* NF-54 strain	Cytotoxicity assay	Aqueous-methanolic extract of CV stem exhibited the most potent anti-malarial effect with IC_{50}=7.5ug/mL follow by methanolic extract of CV leaf with IC_{50}=32.0ug/mL.	(23)
	Swiss inbred mice	Combination of aqueous-methanolic and methanolic extract	Stem, Leaf	*Plasmodium berghei* strain	Comparison of parasite suppression against standard drug chloroquine	87.8% of parasites treated with combined CV extract showed signs of suppression on Day 8 compared to chloroquine which showed complete suppression.	
	In vitro	Methanol	Leaf	*Plasmodium falciparum* 3D7 strain	Malarial SYBR Green I fluorescence-based (MSF) assay	*C. vespertilionis* leaf methanolic extract showed moderate antimalarial activity (IC_{50}=43.87±2.04ug/mL) compared to potent antimalarial drug Artemisinin (IC_{50}= 4.0±0.22ng/mL)	(20)
Antioxidant	2.5, 3.35, 5, 10, 50mg/L	Methanol (free phenolic, soluble bound and insoluble bound)	Leaf	DPPH assay, Follin-Ciocalteu method	Antioxidant radical scavenging assay was conducted	Insoluble bound *C. vespertilionis* extract showed highest antioxidant properties.	(28)
	1mg/mL	Ethanol, aqueous	Leaf	Follin-Ciocalteu method, aluminium chloride colorimetric	Total phenolic content and total flavonoid content was screened	Both TPC and TFC for ethanolic *C. vespertilionis* extract was higher than aqueous extract, even though the percentage yield for ethanolic extract was lower.	(22)

expression and pro-inflammatory cytokine production (25).

Antioxidant activity

Phenolic compounds are vital for plant defence, acting as an antioxidant or antimicrobial agent to ensure the plants' survival (26). In response to specific environmental conditions, plants synthesise various phytochemicals to protect themselves from threats such as microbes and animals or to continue basic physiological functions. Some groups of compounds that are classified as antioxidants are alkaloids, flavonoids, phenolics and more. To date, several assays have been used to detect these groups of antioxidants in the plant, such as β-Carotene assay and total phenolic content assay by Folin-Ciocalteu reagent. *C. vespertilionis* have been shown to have high antioxidant properties (27).

A study determined the total phenolic contents and antioxidant scavenging activity of *C. vespertilionis* methanolic extract by the Follin-Ciocalteu method and DPPH assay (28). They concluded that the highest phenolic content was seen in the insoluble bound extract. At the highest concentration of 50 mg/mL, the extract that showed the highest percentage of inhibition in radical scavenging capacity was the soluble bound extract.

Prior to testing the cytotoxic properties of *C. vespertilionis* leaf ethanolic extract, a group of researchers first tested the TPC and TFC between the ethanolic and aqueous extract using the Follin-Ciocalteu method and aluminium chloride colourimetric method, respectively. They discovered that the TPC and TFC content of the ethanolic *C. vespertilionis* was higher than the aqueous extract. They also identified isoorientin as a major phytochemical compound in the extracts (22). Isoorientin is a common C-glycosyl flavone, luteolin-6-C glucoside, found in many plants and studied for its anti-inflammatory, anti-cancer and antioxidant properties (29–31).

Phytochemistry

Plant metabolites can be divided into primary and secondary metabolites (33). Primary metabolites contribute to the plant's growth, and compounds in this group generally consist of carbohydrates, amino acids, fatty acids, and others (34). On the other hand, secondary metabolites give the plant characteristics such as colour or protection against animals and other predatory organisms (35). Some examples of compounds under this category are flavonoids, alkaloids and terpenoids (36).

In past studies, methanolic extracts of C. vespertilionis leaves showed the presence of alkaloids, flavonoids, glycosides, tannins, diterpenes, coumarin and quinine (16). Table III shows the various phytoconstituents that are found in *C. vespertilionis*.

Table III: Phytoconstituents found in *C. vespertilionis* plant

Active constituent		Part of plant	Reference
Flavonoids	3,4-Dihyro-4-(4'-hydorxy-phenyl)-5,7)-dihydroxy coumarin, sternbin, kaempferol, quercetin, kuchecarpins C, 8-C-prenyl kaempferol, kuwanon L	Root	(9)
	2'-hydroxygenestin, orobol, 2,3-dihydro-2'-hydroxygenestin, quercetin-3-ß-glucoside, catechin-3-O-ß-D-glucopyranoside	Stem & leaf	(23)
	Isoorientin	Leaf	(22)
	mono- and dihydroxyflavones,C-glycosylflavone derivatives, flavone-C,O-diglycosides, and flavonol-3-O-glycosides	Leaf	(3)
Quinones	Fallacinol, alizarin, purpurin, rhein, denbinobin	Root	(9)
Coumarins	5,7-Dihydroxy chromone, wedelolactone	Root	(9)
Phenolic acids	Sanleng acid	Root	(9)
	D:C-friedoolean-8-en-29a-ol, ursolic acid methyl ester, oleanolic acid methyl ester, erythrodiol, geraniol	Stem & leaf	(23)
	Caffeoyl glucoside, Crotonylated derivative of vanillic acid glucosyl ester, Caffeoylglycolic acid methyl ester, Dihydroxybenzoic acid crotonyl hexoside, Vanillic acid 4-O-glucoside, p-coumaroylquinic acid, p-hydroxybenzoic acid 4-O-glucoside, Caffeic acid 4-O-glucoside, Isopropyl derivative of caffeoylglycolic acid methyl ester, Dihydroxybenzoic acid malonyl hexoside, p-coumaric acid 4-O-glucoside, Ferulic acid 4-O-glucoside, Dihydroxybenzoic acid dimalonyl hexoside	Leaf	(3)
Steroids	Stigmasterol, ß-sitosterol acetate, Я-sitosterol	Stem & leaf	(23)
Others	Christene, christanoate	Stem & leaf	(23)
	benzyltetrahydroisoquinoline alkaloids, hydroxyjasmonic acid derivatives, phenethyl derivatives, monoacylglycerols, fatty acid amides, chlorophyll derivatives, carotenoids,organic acids, nucleoside, and amino acids.	Leaf	(3)

Flavonoids

One of the most commonly reported groups of phytochemicals that have been reported in studies involving *C. vespertilionis* extracts was flavonoids. This polyphenolic group is widely found in many fruits and vegetables (37). Some upcoming studies involving flavonoids mainly focus on their anti-inflammatory, antioxidant, anti-cancer, and antimicrobial properties. Several studies have reported the presence of flavonoids in the root, stem, and leaf extracts of *C. vespertilionis*, regardless of its extraction method (9,22,23). Although the studies on this particular area are still sparse, it is pointing towards a good direction for more future opportunities for this plant. Below are the studies that were conducted using various parts of the *C. vespertilionis* plant.

Root
A study found that the root extract of *C. vespertilionis* was more potent in terms of cytotoxicity compared to leaf extracts. Flavonoids, quinones, coumarins, and phenolic acids were some of the compounds reported found in the root (9).

Leaf
The most common part of the *C. vespertilionis* plant that was studied was the leaf. It was reported to be containing flavonoids, phenolic acids, and steroids (22,23). Although not as strong as root extracts, a study showed that the methanolic leaf extract exhibited selective cytotoxicity, whereby breast cancer cell lines were significantly affected by treatment but did not inhibit the growth of noncancerous 3T3 cell lines (20).

Side effects
In an experiment, samples of the liver that have been treated with the *C. vespertilionis* extract exhibited signs of necrosis, degeneration and inflammation in the histopathology examination (12). The degeneration of liver cells is caused by excess accumulation of glycogen, predominantly of the monoparticulate form, following consumption of low doses of the extract. However, upon further inspection, the degree of regeneration on the liver tissue is greater than the damage left by the consumption of the extract. The 28-day study concluded that the ethanolic extract of *C. vespertilionis* is safe for oral consumption. However, long-term toxicity testing still unknown (12).

Extraction Methods
The standard extraction methods are via methanolic, ethanolic, and aqueous. A study used supercritical fluid extraction method to obtain the oils from the red and green *C. vespertilionis* leaves. The process took about 60 minutes. The resulting oil was then submitted for qualitative analysis using Liquid Chromatography-Mass Spectrometry (LCMS) to identify the active compounds (24).

In experiments that required the extract to be used in vitro, researchers applied the ethanolic and aqueous extraction by first obtaining the powder sample of the *C. vespertilionis* leaves and using solvents or water to obtain the residue and supernatant. This extract is then used to observe the synergy between *C. vespertilionis* extract and the chemotherapy drug, cyclophosphamide (22).

In another study, *C. vespertilionis* was extracted via 90% ethanol, which resulted in a dark greenish-brown extract. It was then concentrated using a Rota evaporator under reduced pressure. For animal studies, the extract was lyophilised and prepared in 5% Dimethyl sulfoxide (DMSO) (12).

Extraction is a key stage in the process of getting bioactive components from plant sources. Several solvents with differing polarities must be utilised to achieve varied phenolic compounds extraction precision utilised (37). Solvents with high polarities, such as methanol, have high effectiveness as antioxidants. Methanol was much more successful than ethanol in extracting the considerable amount of phenolic compounds found in walnut fruits (38). Hexane: ethyl acetate extract of *C. vespertilionis* has been shown to possess the greatest ferric reducing antioxidant power (FRAP) capacity and a-glucosidase inhibition (14). However, extraction using ethyl acetate: methanol showed the most potential in 2, 2- diphenyl-1-picrylhydrazyl (DPPH) radical scavenging inhibition (14).

CONCLUSION

Although a handful of publications ranging from manuscripts to news articles have been documenting the use and history of *C. vespertilionis*, we found that there are still a few gaps of knowledge that could be explored with this remarkable plant. To date, most research published has focused on the anti-cancer, antioxidant and anti-malarial aspect of this plant. However, the pharmacological research may also open to other possibilities. There are communities utilising this herb traditionally for other ailments such as hypertension, diabetes and even a simple fever, with less in vivo studies conducted. In this review paper, most of the experiments are either using chemical assays or in vitro studies. Another aspect that can be explored is the gene-altering capabilities of the *C. vespertilionis* plant, hence opening the future of molecular research.

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