Role of Vacha (*Acorus calamus* Linn.) in Neurological and Metabolic Disorders: Evidence from Ethnopharmacology, Phytochemistry, Pharmacology and Clinical Study

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**Abstract:** Vacha (*Acorus calamus* Linn. (Acoraceae)) is a traditional Indian medicinal herb, which is practiced to treat a wide range of health ailments, including neurological, gastrointestinal, respiratory, metabolic, kidney, and liver disorders. The purpose of this paper is to provide a comprehensive up-to-date report on its ethnomedicinal use, phytochemistry, and pharmacotherapeutic potential, while identifying potential areas for further research. To date, 145 constituents have been isolated from this herb and identified, including phenylpropanoids, sesquiterpenoids, and monoterpenes. Compelling evidence is suggestive of the biopotential of its various extracts and active constituents in several metabolic and neurological disorders, such as anticonvulsant, antidepressant, antihypertensive, anti-inflammatory, immunomodulatory, neuroprotective, cardioprotective, and anti-obesity effects. The present extensive literature survey is expected to provide insights into the involvement of several signaling pathways and oxidative mechanisms that can mitigate oxidative stress, and other indirect mechanisms modulated by active biomolecules of *A. calamus* to improve neurological and metabolic disorders.

**Keywords:** *Acorus calamus*; ethnomedicinal; phytochemistry; toxicity; pharmacological action; clinical trial; neuroprotective; neurological; metabolic application

1. Introduction

Globally, an estimated 450 million people are suffering from mental disorders and about 425 million are known diabetics [1,2]. In 2016, 650 million adults were obese and about 23.6 million people were estimated to die of cardiovascular diseases (CVDs) by the year 2030 [3]. Metabolic disorders are characterized by hypertension, hyperglycemia, abdominal obesity, and hyperlipidemia, which may worsen the neurological disease risk. Improper diet (high calorie intake), lifestyle (e.g., smoking, chronic alcohol consumption, sedentary habits), and/or low level of nitrosamines (through processed food, tobacco smoke, and nitrate-containing fertilizers) affect the liver and can further lead to fatty liver disease [4,5]. In this condition, fatty changes may be due to increased production or decreased use of fatty
acids, which may lead to inflammatory injury of hepatocytes, where inflammatory mediators, such as cytokines and interleukins, are released, which, along with lower adipokines, may eventually develop hepatic insulin resistance [6]. The same pathology also mediates diabetes, obesity, and peripheral insulin resistance. Insulin resistance also promotes the release of ceramides and other toxic lipids which enter the circulation and cross the blood–brain barrier leading to brain insulin resistance, inflammatory changes, and further progression to neurodegeneration and neurological disorders (Figure 1) [7].

Acorus calamus Linn. (Acoraceae), also known as Vacha in Sanskrit, is a mid-term, perennial, fragrant herb which is practiced in the Ayurvedic (Indian traditional) and the Chinese system of medicine. The plant’s rhizomes are brown in color, twisted, cylindrical, curved, and shortly nodded. The leaves are radiant green, with a sword-like structure, which is thicker in the middle and has curvy margins (Figure 2) [8]. Several reports ascertained a wide range of biological activities involving its myriad of active phytoconstituents. In this sense, the intent of this review is to assemble and summarize the geographical distribution, ethnopharmacology, phytochemistry, mechanism of action of A. calamus along with preclinical and clinical claims that are relevant to manage neurological and metabolic disorders. To the best of our knowledge, so far, none of the published reviews has described all the characteristics of this medicinal plant [9–11]. The present report is expected to produce a better understanding of the characteristics, bioactivities, and mechanistic aspects of this plant and to provide new leads for future research.
Figure 2. Photographs of *Acorus calamus*: (A) Natural habitat; (B) Fresh rhizome; (C) Dried rhizome.

2. Methodology

The literature available in the Ayurvedic classical texts, technical reports, online scientific records such as SciFinder, Google Scholar, MEDLINE, EMBASE, Scopus directory were explored for ethnomedicinal uses, geographical distribution, phytochemistry, pharmacology, and biomedicine by applying the following keywords: “*Acorus calamus*”, “Vacha”, “Medhya”, “neuroprotective”, “phytochemistry”, “obesity”, “oxidative stress”, “anticonvulsant”, “antidepressant”, “antihypertensive”, “anti-inflammatory”, “immunomodulator”, “antioxidant”, “diabetes”, “mechanism of action” with their corresponding medical subject headings (MeSH) terms using conjunctions OR/AND. The search was focused on identifying Ayurvedic claims in the available ethnomedicinal, phytochemical, preclinical, clinical, and toxicity reports to understand the role of *A. calamus* in neurological and metabolic disorders. This search was undertaken between January 2018 and January 2020. Searches were restricted to the English language. The search methodology as per the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) is stipulated in the flowchart in Figure 3.

Figure 3. Flowchart of the selection process.
3. Geographical Distribution

*A. calamus* grows in high (1800 m) and low (900 m) altitudes and it is found to be geographically available in 42 countries [8]. Furthermore, as per the Global Biodiversity Information Facility records [12], the distribution of this plant in several parts of the world, as well as in India, is highlighted in Figure 4.

![Figure 4. Distribution of *A. calamus* worldwide and in India.](image)

4. Ethnomedicinal Use

This plant is being practiced traditionally in the Indian Ayurvedic tradition, as well as in the Chinese system of medicine for analgesic, antipyretic, tonic, anti-obesity, and healing purposes; it is highly effective for skin diseases, along with neurological, gastrointestinal, respiratory, and several other health disorders. Rhizomes and leaves are found to be profusely practiced in the form of infusion, powder, paste, or decoction [13–72]. The ethnomedicinal uses of the *A. calamus* are detailed in Table 1.

*A. calamus* rhizomes and leaves are also used as an active pharmaceutical ingredient in various Ayurvedic formulations (Table 2).
Table 1. Ethnomedicinal use of *A. calamus* in various countries.

| Country | Ailment/Use                                      | Part Used/ Dosage Form                                                                 | Route of Administration | References |
|---------|------------------------------------------------|---------------------------------------------------------------------------------------|-------------------------|------------|
|         | Eczema                                          | The paste of *A. calamus* rhizomes are given with the paste of *Curcuma aromatica* rhizomes and *Azadirachta indica* leaves | Oral                    | [13]       |
|         | Skin diseases                                   | Rhizomes paste *A. calamus* and *C. aromatica* are applied with the seed paste of *Argemone Mexicana* | Oral                    |            |
|         | Cough, stuttering, ulcer, fever, dermatitis, scab, sores | Rhizomes paste of *A. calamus* is given to children with mother’s milk, *Myristica fragrance*, and *Calunarejan spinosus fruits* | Oral                    | [14]       |
|         | Cold, cough, and fever                          | Two teaspoonfuls of herbal powder containing *A. calamus* rhizomes, *Boerhaavia diffusa* roots, *Calonyction muriculum* flower pedicles, *Ipomoea muricate* seeds, *Senna* leaves, *Cassia fistula* fruits pulp, *Curcuma longa* rhizomes, *Helicteres isora* fruits, and *Mentha arvensis* leaves, black pepper is taken with lukewarm water | Oral                    | [15]       |
| India   | Gastric disorders                               | *A. calamus* rhizomes paste is given with cow milk                                   | Oral                    | [16]       |
|         | Carminative, flavoring, tonic, and head lice infestation | Infusion of a dried rhizomes (collected and stored in the autumn season)              | Oral                    | [17–19]    |
|         | Epilepsy, dysentery, mental illnesses, diarrhea, kidney and liver disorders | *A. calamus* rhizomes paste is given with honey                                        | Oral                    | [20]       |
|         | Wounds, fever, body pain                        | Rhizomes                                                                             | Oral                    | [21,22]    |
|         | Dysentery                                       | Fresh ground rhizomes is mixed with hot water and given for 3 days                   | Oral                    | [23]       |
|         | Stimulant                                       | Dry powder of *A. calamus* is given with honey                                        | Oral                    | [24]       |
|         | Injuries                                        | External application of the *A. calamus* rhizomes paste                              | Oral                    | [25]       |
|         | Stomachache                                     | Ash of the *A. calamus* rhizomes paste                                              | Oral                    | [26]       |
|         | Otitis externa                                  | *A. calamus* roots paste is given with coconut husk juice                            | Dermal                  | [27]       |
|         | Lotion                                          | Fresh leaves of *A. calamus*                                                        | Dermal                  | [28]       |
|         | Cough, cancer, and fever                        | *A. calamus* roots juice is given with honey and *MyristicaDactyloides*            | Dermal                  | [29]       |
| Country | Ailment/Use | Part Used/ Dosage Form | Route of Administration | References |
|---------|-------------|------------------------|------------------------|------------|
| Pakistan | Colic and diarrhea | Whole plant | Oral | [35] |
| Nepal | Blood pressure | Roots infusion of *A. calamus* | Oral | [36] |
| Nepal | Cough, headache, snake bite, sore throat, and pain | Rhizomes | | [37] |
| Nepal | Dysentery | Rhizomes juice is given with hot water | | [37] |
| Malaysia | Rheumatism, diarrhea, dyspepsia, and hair loss | Whole plant | | [39] |
| Tibet | Fever, gastrointestinal | Dried rhizomes is given with *Saussurea lappa, Ferula foetida, Terminalia chebula, Cuminum cuminum, Inula racemosa,* and *Zingiber officinale* | | [40] |
| Tibet | Cancer | Rhizomes | | [41] |
| Country          | Ailment/Use                                      | Part Used/ Dosage Form                      | Route of Administration | References |
|------------------|-------------------------------------------------|--------------------------------------------|-------------------------|------------|
| China            | Gastrointestinal, respiratory, neuroprotective, analgesic, contraceptive, cancer | Rhizomes                             |                         | [42–44]    |
|                  | Antipyretic and ear-related disease              | Rhizomes given with squeezed *Coccinia cordifolia* stems along with water |                         |            |
|                  | Detoxification                                   | Rhizomes with vinegar, *Alpinia galanga, Zingiber purpureum* |                         | [45]       |
|                  | Analgesic                                        | Herbal baths of the rhizome                | External                |            |
|                  | Hemorrhage                                       | Rhizomes paste                            |                         | [46]       |
|                  | Aphrodisiac                                      | Rhizomes                                  | Oral                    | [47]       |
|                  | Hallucination                                    | Rhizomes are mixed with Indian hemp and *Podophyllum pleianthum* |                         | [48]       |
|                  | Fair skin                                        | Leaves of *A. calamus* are given with *Artemisia vulgaris* | Dermal                  | [49]       |
| Indonesia        | Gastrointestinal                                 | Rhizomes                                  |                         | [50]       |
|                  | Rhizomes blended with chalk and magnesium oxide  |                                           |                         | [51]       |
| England          | Gastrointestinal, antibacterial, analgesic       | Rhizomes                                  |                         | [52]       |
|                  | Neurological, dysentery, and chronic catarrh     | Rhizomes are given with *Gentiana campestris* L. |                         | [53]       |
|                  | Malaria                                          |                                           | Oral                    | [54,55]    |
| Europe           | Obesity, influenza, gastrointestinal, respiratory |                                           |                         |            |
| Republic of      | Tooth powder, gastrointestinal, tonic, aphrodisiac | Rhizomes                                  |                         | [56]       |
| South Africa     |                                                 |                                           |                         |            |
| Sweden           | Liquor                                           |                                           |                         | [57]       |
| Germany          | Increases menstrual flow, gastrointestinal       |                                           |                         | [58,59]    |
| Java             | Lactation                                        |                                           |                         | [60]       |
| Country       | Ailment/Use                                      | Part Used/ Dosage Form                  | Route of Administration | References |
|--------------|-------------------------------------------------|----------------------------------------|-------------------------|------------|
| Lithuania    | Chest pain, diarrhea                            | Rhizomes and leaves are taken with sugar|                         | [52]       |
|              | Relieves pain, gout, rheumatism                 | Leaves decoction                       | External                | [61]       |
| New Guinea   | Miscarriage                                      |                                        |                         | [62]       |
| Philippines  | Gastrointestinal, rheumatism                     |                                        |                         | [56]       |
| Russia       | Typhoid, syphilis, baldness, fever, cholera      |                                        | Oral                    | [63]       |
| Thailand     | Blood purifier, fever                            |                                        |                         | [64]       |
| Turkey       | Wound healing, cough, tuberculosis              | Rhizomes                               | External and oral       | [61]       |
|              | Gastrointestinal                                |                                        |                         | [65,66]    |
| Arab countries| Gastrointestinal, tuberculosis                  |                                        |                         | [67,68]    |
| Brazil       | Destroys parasitic worms                        |                                        |                         | [68]       |
| Argentina    | Dysmenorrhea                                     |                                        | Oral                    | [69]       |
| United States| Gastrointestinal, abortifacient, stimulant, tonic, respiratory disorder | Rhizomes           |                         | [70]       |
| Korea        | Improves memory and life span                    |                                        |                         | [71]       |
| Sri Lanka    | Cough, worm infestation                         | Rhizomes paste are given with milk     |                         | [72]       |
Table 2. Pharmaceutical products of *A. calamus* available in the market.

| Medicine/Formulations          | Indications/Use                                  | Manufacturers                      |
|-------------------------------|-------------------------------------------------|-----------------------------------|
| Pilochek tablets              | Hemorrhoids                                     |                                   |
| Brahmi Rasayan                | Nervine tonic                                   | Dabur India Limited               |
| Mahasudarsan Churna           | Malaria                                         |                                   |
| Janma Ghunti Honey            | Babies growth, Constipation, Diarrhea           |                                   |
| Brahmi Pearls capsules        | Brain Nourisher                                 |                                   |
| GT capsules                   | Osteoarthritis, osteoporosis, hyperlipidemia     | Kerala Ayurveda                   |
| Histantin tablets             | Anti-allergic                                   |                                   |
| Santhwanam oil                | Antioxidant, rejuvenate                         |                                   |
| Mahathikthaka Ghrita capsules | Skin disease, malabsorption syndrome            | Florida Herbal Pharmacy           |
| Calamus root tincture         | Stimulates the digestive system                 |                                   |
| Vacha capsules                | Food supplements                                | DR Wakde’s Natural Health Care, London |
| Mentat tablets and syrup      | Nervine tonic                                   |                                   |
| Abana                         | Cardiovascular disorders, hyperlipidemia, dyslipidemia | Himalaya Herbal Healthcare       |
| Mentat tablets and Syrup      | Anxiety, depression, insomnia                   |                                   |
| Muscle & Joint Rub            | Backaches, muscular sprains, pain               |                                   |
| Anxocare                      | Anxiety                                         |                                   |
| Erina-EP                      | Ectoparasites                                   |                                   |
| Himpyrin, Himpyrin Vet        | Analgesic and anti-inflammatory                 |                                   |
| Scavon Vet                    | Anti-bacterial, anti-fungal                      |                                   |
| Vacha powder                  | Brain tonic, improves digestion, and prevents nausea | Bixa Botanical                   |
| Amalth                        | Herbal supplements                              | Mcnow Biocare Private Limited     |
| Sunarin capsules              | Anal fissures, piles, rectal inflammation, congestion | SG Phyto Pharma                 |
| Medicine/Formulations                        | Indications/Use                                      | Manufacturers                                |
|---------------------------------------------|-----------------------------------------------------|----------------------------------------------|
| Dr Willmar Schwabe India *Acorus calamus* mother tincture | Intestinal worms and stomach disorders, fever, nausea | Dr Willmar Schwabe India Pvt Ltd.            |
| Himalayan calamus root essential oil         | Pain relief and calm mind                            | Naturalis Essence of Nature                  |
| Calamus oil                                 | Body, skin care, hair growth                         | Kazima Perfumers                             |
| Calamus root powder                         | Mental health problems                               | Heilen Biopharm                              |
| Winton tablets and syrup                    | Reduce tension, stress, and anxiety                  | Scortis Healthcare                           |
| Chesol syrup                                | Muscular aches and pains, chest colds, and bronchitis| J & J Dechane Laboratories Private Limited   |
| Enzo Fast                                   | Acidity, gastritis, flatulence, indigestion          | Naturava                                     |
| Dark Forest Vekhand powder                  | Abdomen pain, worms (infants)                        | Simandhar Herbal Pvt. Ltd.                  |
| Nervocare                                   | Insomnia                                            | Deep Ayurveda                                |
| Antress tablets                             | Anxiety and stress disorders                         | Ayursun Pharma                               |
| Grapzone syrup                              | Mental wellness                                      | Alna Biotech Pvt Ltd.                        |
| Memoactive syrup                            | Improves memory power                                | Aayursh Herbal India                         |
| Smruthihills capsules                       | Stress, anxiety, adaptogenic                        | Ayush Arogyam                                |
| Gastrin capsules                            | Gastritis, dyspepsia                                 | Sarvana Marundhagam                          |
| Pigmento tablets                            | Leukoderma or vitiligo                               | Charak Pharma                                |
| Paedritone drops                            | Digestive functions                                  |                                              |
| Vacha Churna                                | Brain tonic, digestion, nausea                       | Sadvaidyasala                                |
| Alert capsules                              | Immunomodulator, anxiety                             | Vasu Healthcare                              |
| Brento tablets                              | Increasing cognitive functions                       |                                              |
| Livotrit Forte                              | Hepatitis, jaundice                                  | Zandu Realty Limited                         |
| Zanduzyme                                   | Indigestion and dyspepsia                            |                                              |
| Medicine/Formulations       | Indications/Use                              | Manufacturers                  |
|----------------------------|---------------------------------------------|--------------------------------|
| Vedic Slim                 | Anti-obesity                                | Vedic Bio-Labs Pvt. Ltd.       |
| Hinguvachaadi Gulika       | Anorexia, indigestion, appetite loss         | Nagarajuna Pvt. Ltd.           |
| Nilsin capsules            | Sinusitis and allergic rhinitis             | Phytomarketing                |
| Norbeepee tablet           | Hypertension                                | AVN Formulations              |
| Sooktyn tablet             | Antacid, antispasmodic                      | Alarsin Pharma Pvt. Ltd.       |
| Deonac oil                 | Pain relieving oil                          | Doux Healthcare Pvt. Ltd.      |
| Smrutsagar Rasa            | Memory enhancer                             | Shree Dhootpapeshwar Limited   |
| Yogaraj Guggul             | Vitiligo, anorexia, indigestion, loss of appetite |                              |
| Kankayan Bati              | Gastritis, flatulence, dyspepsia            | Baidyanath Pvt. Ltd.           |
| Brahmi Ghrita              | Insanity and memory issues                  |                                |
| Fat Go                     | Controls high cholesterol level             | Jolly Healthcare               |
| Divya Medha Vati           | Improves memory power                       | Patanjali Ayurveda             |
| Divya Mukta Vati           | High blood pressure                         |                                |

Table 2. Cont.
5. Phytochemistry

The phytochemical investigation of this plant has been ongoing since the year 1957 [73,74]. To date, about 145 compounds were isolated from *A. calamus* rhizomes and leaves, viz. phenylpropanoids, sterols, triterpene glycosides, triterpenoid saponins, sesquiterpenoids, monoterpenes, and alkaloids (Table 3). Amongst those, phenylpropanoids (chiefly, asarone and eugenol) and sesquiterpenoids have been considered the principal effective compounds of *A. calamus*. Chemical structures of isolated compounds from *A. calamus* are illustrated in Figure 5.

Figure 5. Cont.
Figure 5. Cont.
Chemical structures of isolated compounds from A. calamus.

5.1. Phenylpropanoids

Phenylpropanoids have an aromatic ring with a structurally diverse group of phenylalanine-derived secondary plant metabolites (C₆–C₃), like α-asarone, β-asarone, eugenol, isoeugenol, etc. [75]. A number of phenylpropanoids have been identified from A. calamus rhizome and leaves (1-45). α and β-asarone isolated from the rhizome are the predominant compounds present in this plant. A series of aromatic oils from the rhizome with diverse structures are also reported [74–98].
### Table 3. Chemical compounds isolated from different botanical parts of *A. calamus*.

| Classification | Compound No. | Chemical Ingredient            | Methods of Characterization | Parts/Extract                          | References       |
|----------------|--------------|--------------------------------|----------------------------|----------------------------------------|------------------|
| Phenylpropanoids | 1            | α-Asarone                       | GC-FID, GC-MS              | Rhizomes/n-hexane, aqueous, methanol, ethanol | [74,78,84,89–91] |
|                 | 2            | β-Asarone                       |                            |                                        |                  |
|                 | 3            | γ-Asarone                       |                            |                                        |                  |
|                 | 4            | Eugenyl acetate                 |                            |                                        |                  |
|                 | 5            | Eugenol                         |                            |                                        | [74,78,91]       |
|                 | 6            | Isoeugenol                      |                            |                                        | [92]             |
|                 | 7            | Methyl eugenol                  |                            |                                        | [74,78,91,94]    |
|                 | 8            | Methyl isoeugenol               |                            |                                        |                  |
|                 | 9            | Calamol                         |                            |                                        |                  |
|                 | 10           | Azulene                         |                            |                                        |                  |
|                 | 11           | Eugenol methyl ether            |                            |                                        | [74,78,91]       |
|                 | 12           | Dipentene                       |                            |                                        |                  |
|                 | 13           | Asaronaldehyde                  |                            |                                        |                  |
|                 | 14           | Terpinolene                     |                            |                                        |                  |
|                 | 15           | 1,8-cineole                     |                            |                                        |                  |
|                 | 16           | (E)-isoeugenol acetate          |                            |                                        | [89]             |
|                 | 17           | (E)-methyl isoeugenol           |                            |                                        |                  |
|                 | 18           | Cis-methyl isoeugenol           | GC-FID, GC-MS             | Rhizomes/n-hexane, ethyl acetate       | [92]             |
|                 | 19           | Euasarone                       |                            |                                        |                  |
|                 | 20           | Cinnaldehyde                    |                            |                                        |                  |
|                 | 21           | Cyclohexanone                   | GC-MS                     | Rhizomes/hexane                        | [94]             |
|                 | 22           | Acorin                          |                            |                                        |                  |
|                 | 23           | Isoasarone                      | NMR                       | Rhizomes/chloroform                    | [95]             |
|                 | 24           | Safrole                         |                            |                                        |                  |
| Classification | Compound No. | Chemical Ingredient | Methods of Characterization | Parts/Extract       | References |
|----------------|--------------|---------------------|----------------------------|---------------------|------------|
| Phenylpropanoids | 24           | Safrole              |                           |                     |            |
|                 | 25           | Z-3-(2,4,5-trimethoxyphenyl)-2-propenal | FTIR, NMR               | Rhizomes/ethanol    | [96]       |
|                 | 26           | 2,3-dihydro-4,5,7-trimethoxy-1-ethyl-2-methyl-3-(2,4,5-trimethoxyphenyl) indene | FTIR, NMR               | Rhizomes/ethanol    | [96]       |
|                 | 27           | (Z)-asarone          |                           |                     |            |
|                 | 28           | (E)-caryophyllene    |                           | Leaves/n-hexane     | [97]       |
|                 | 29           | Estragole            |                           |                     |            |
|                 | 30           | Carvacrol            |                           |                     |            |
|                 | 31           | 2-cyclohexane-1-one  |                           |                     |            |
|                 | 32           | Naphthalene          |                           |                     |            |
|                 | 33           | γ-Cadinene           |                           |                     |            |
|                 | 34           | Aristolene           |                           |                     |            |
|                 | 35           | 1(5),3-aromadenediadiene | GC-MS               | Rhizomes/aqueous    | [98]       |
|                 | 36           | 5-n-butyltetraline   |                           |                     |            |
|                 | 37           | 4,5-dehydro-isolongifolene |             |                     |            |
|                 | 38           | Calarene             |                           |                     |            |
|                 | 39           | Isohomogenol         |                           |                     |            |
|                 | 40           | Zingiberene          |                           |                     |            |
|                 | 41           | α-Calacorene         |                           |                     |            |
|                 | 42           | 5,8-dimethyl isouquinoline |             |                     |            |
|                 | 43           | Cyclohexane methanol |                           |                     |            |
|                 | 44           | Longifolene          |                           |                     |            |
|                 | 45           | Isoelemicin          |                           |                     |            |
Table 3. Cont.

| Classification | Compound No. | Chemical Ingredient | Methods of Characterization | Parts/Extract | References |
|----------------|--------------|---------------------|----------------------------|---------------|------------|
| Sesquiterpenoids | 46 | Calamene | | | |
| | 47 | Calamenenol | | | |
| | 48 | Calameone | | | |
| | 49 | Preisocalamendiol | | | |
| | 50 | 1,4-(trans)-7(trans)-acorenone | | | |
| | 51 | 1,4-(cis)-1,7-(trans)-acorenone | | | |
| | 52 | 2,6 diepishyobunone | | [93] | |
| | 53 | α-Gurjunene | | | |
| | 54 | β-Gurjunene | | | |
| | 55 | α-Cedrene | | | |
| | 56 | β-Elemene | | | |
| | 57 | β-Cedrene | | [98] | |
| | 58 | β-Caryophyllene | | | |
| | 59 | Valencene | | | |
| | 60 | Viridiflorene | | | |
| | 61 | α-Selinene | GC-FID, GC-MS | | [89,93] |
| | 62 | δ-Cadinene | | | [93] |
| | 63 | α-Curcumene | | | |
| | 64 | Shyobunone | GC-MS | | [84,93,99,100] |
| | 65 | Isoshyobunone | | | [93,99,101] |
| | 66 | Caryophyllene oxide | | | [93] |
| | 67 | Humulene oxide II | GC-FID, GC-MS | | [89,93] |
| | 68 | Elemol | | | |
| | 69 | Cedrol | | | |
| | 70 | Spathulenol | GC-MS | | [93] |
| | 71 | Acorenone | | | |
| | 72 | α-Cadinol | | | |
| | 73 | Humulene epoxide II | | GC-FID, GC-MS | | [89] |
| | 74 | α-Bisabolol | | | |
| Classification | Compound No. | Chemical Ingredient | Methods of Characterization | Parts/Extract | References |
|----------------|-------------|---------------------|----------------------------|---------------|------------|
| Sesquiterpenoids | 75 | Asaronaldehyde | NMR | Rhizomes/chloroform | [95] |
| | 76 | Calamusenone | | | |
| | 77 | Isocalamendiol | | | |
| | 78 | Dehydroxyiso-calamendiol | GLC, IR, NMR | Rhizomes/petroleum ether | [99] |
| | 79 | Epishyobunone | | | |
| | 80 | Acorone | | Rhizomes/hydro alcoholic | [100] |
| | 81 | Neo-acorane A | | | |
| | 82 | Acoric acid | NMR | Rhizomes/ethanol | [102] |
| | 83 | Calamusin D | | | |
| | 84 | 1β,5α-Guaiane-4β,10α-diol-6-one | | | [103] |
| | 85 | Dioxosarcoquaiacol | HPLC | Rhizomes/petroleum ether | [101] |
| | 86 | 7-tetracycloundecanol,4,4,11,11-tetramethyl | | | [84] |
| | 87 | 4α,7-Methano-4α-naphth[1,8-a-b]oxirene, | GC-MS | | |
| | 88 | Spalthulenol | | Rhizomes/aqueous | [98] |
| | 89 | Vulgarol B | | | |
| | 90 | Tatran A | | | |
| | 91 | Acoramone | | | |
| | 92 | 2-hydroxyacorenone | | | |
| | 93 | 4-(2-formyl-5-methoxymethyl pyrrol-1-yl) butyric acid methyl ester | | | |
| | 94 | 2-acetoxyacorenone | HPLC, NMR | Rhizomes/95% ethanol | [104] |
| | 95 | Acoramol | | | |
| | 96 | N-transferuloyl tyramine | | | |
| | 97 | Tatarinoid A | | | |
| | 98 | Tatarinoid B | | | |
| | 99 | Acortatarin A | | | |
Table 3. Cont.

| Classification | Compound No. | Chemical Ingredient | Methods of Characterization | Parts/Extract | References |
|----------------|--------------|---------------------|-----------------------------|---------------|------------|
| Monoterpenes   | 100          | α-Pinene            |                             |               | [74,78,91,93] |
|                | 101          | β-Pinene            |                             |               |            |
|                | 102          | Camphene            |                             |               | [74,78,91,93,98] |
|                | 103          | α-Cymol             |                             |               | [98]       |
|                | 104          | p-Cymene            | GC-FID, GC-MS               | Rhizomes, roots/aqueous | [98]       |
|                | 105          | γ-Terpinene         |                             |               |            |
|                | 106          | α-Terpinolene       |                             |               |            |
|                | 107          | Anethole            |                             |               | [98]       |
|                | 108          | Thymol              |                             |               |            |
|                | 109          | Isoaromadendrene epoxide |                     |               |            |
|                | 110          | Camphor             |                             | Rhizome, leaves, roots/aqueous, hexane | [93,97] |
|                | 111          | Sabine              |                             |               | [93]       |
|                | 112          | 2-hexenal           | GC-MS                       |               | [93,98] |
|                | 113          | Limonene            |                             |               | [93]       |
|                | 114          | Cis-linaloloxide    |                             |               | [93]       |
|                | 115          | Cis-sabinene hydrate|                             | Roots/aqueous |            |
|                | 116          | Trans-linalol oxide |                             |               | [93,97] |
|                | 117          | Linalool            |                             |               | [93,97] |
|                | 118          | Terpinen-4-ol       |                             |               |            |
|                | 119          | α-Acoradiene        |                             |               | [93]       |
|                | 120          | β-Acoradiene        |                             |               |            |
|                | 121          | α-Terpinol          |                             |               |            |
|                | 122          | Isoborneol          |                             | Leaves/hexane | [97]       |
| Classification               | Compound No. | Chemical Ingredient                                                                 | Methods of Characterization | Parts/Extract          | References |
|-----------------------------|--------------|--------------------------------------------------------------------------------------|-----------------------------|------------------------|------------|
| Xanthone glycosides         | 123          | 4,5,8-trimethoxy-xanthone-2-O-β-D-glucopyranosyl (1-2)-O-β-D-galactopyranoside        |                             |                        | [83]       |
| Triterpenoid saponins       | 124          | 1α,2α,3β,19α-Tetrahydroxyurs-12-en-28-oic acid-28-O-{β-D-glucopyranosyl (1-2)}-β-D galactopyranoside | NMR                         | Rhizome/ethanol        | [82]       |
|                             | 125          | 22-α,24,29-Tetrahydroxyolean-12-en-3-O-[β-D-arabinopyranosyl (1,3)]-β-D-arabinopyranoside |                             |                        |            |
| Alkaloids                   | 126          | Trimethoxyamphetamine-2,3,5                                                         | GC-MS                       |                        | [84]       |
|                             | 127          | Pyrimidin-2-one,4-[N-methylureido]-1-{amethyl amino carbonloxy methyl}                |                             |                        |            |
| Triterpene glycoside        | 128          | 22-β-[6-deoxy-α-L-rhamnopyranosyl]oxy]-3,23-dihydroxy-, methyl ester, (3β,4β,20α,22β) | NMR                         | Root, Rhizomes/ethyl acetate | [85]       |
| Steroids/Sterols            | 129          | β-daucosterol                                                                         |                             |                        |            |
|                             | 130          | Arginine                                                                              |                             |                        |            |
|                             | 131          | Lysine                                                                                |                             |                        |            |
|                             | 132          | Phenylalanine                                                                         |                             |                        |            |
|                             | 133          | Threonine                                                                             |                             |                        |            |
|                             | 134          | Tryptophan                                                                            |                             |                        |            |
|                             | 135          | α-alanine                                                                             |                             |                        |            |
|                             | 136          | Asparagin                                                                             |                             |                        |            |
|                             | 137          | Aspartic acid                                                                         |                             |                        |            |
|                             | 138          | Norvaline                                                                             |                             |                        |            |
|                             | 139          | Proline                                                                               |                             |                        |            |
|                             | 140          | Tyrosine                                                                              |                             |                        |            |
|                             | 141          | Glutamic acid                                                                         |                             |                        |            |
| Amino acids                 | 142          | Palmitic acid                                                                         | GLC                         | Rhizome/petroleum ether | [88]       |
|                             | 143          | Myristic acid                                                                          |                             |                        |            |
|                             | 144          | Palmitoleic acid                                                                       |                             |                        |            |
|                             | 145          | Stearic acid                                                                           |                             |                        |            |

GC-FID, gas chromatography – flame ionization detector; GC-MS, gas chromatography – mass spectrometry; NMR, nuclear magnetic resonance; FTIR, Fourier-transform infrared spectroscopy; GLC, gas liquid chromatography; IR, infrared spectroscopy; HPLC, high-performance liquid chromatography.
5.2. Sesquiterpenoids

About 44 sesquiterpenes, including lactones, were characterized and identified in A. calamus rhizomes. Sesquiterpene lactones are produced of 3 isoprene units and composed of lactone rings. α-β unsaturated γ-lactonic ring in sesquiterpene lactones is believed to be responsible for pharmacological activity (46-99) [74,78,89,91,93,98–104].

5.3. Monoterpenes

Monoterpenes (C-10) are the simplest class of the terpene series that belongs to two isoprene units (tricyclic, bicyclic, monocyclic, etc.). Monoterpenes can have different functional groups, like aldehydes, ketones, esters, ethers, phenols, and alcohols [80]. These organic compounds emit the characteristic flavor and fragrance of A. calamus leaves and rhizomes (100-122) [74,78,89,91,93,97,98].

5.4. Triterpenoid Saponins

Triterpenoid saponins are made up of a pentacyclic C-30 terpene skeleton as a pillar. Limited reports studying triterpenoid saponins in A. calamus are available, and only two triterpenoid saponins (124, 125) have been isolated from A. calamus rhizomes (Table 3) [85].

5.5. Other Compounds

To date, one xanthone glycoside (123) [82,83], two alkaloids (126-127) [84], one triterpene glycoside (128), one steroid (129) [85], 12 amino acids (130-141) [86,87], and 4 fatty acids (142-145) [88] have been identified in A. calamus rhizomes [83–88].

6. Pharmacological Properties

Diverse bioactivities of A. calamus extracts are evident from preclinical (in vitro and in vivo) and clinical reports, such as antidiabetic, anti-obesity, antihypertensive, antioxidant, anti-inflammatory, immunomodulatory, anticonvulsant, and neuroprotective [105–173]. The summarized information on A. calamus botanical parts, extract type, and their bioactivities in neurological and metabolic disorders is stipulated in Table 4.
Table 4. Preclinical claims of *A. calamus* in neurological and metabolic disorders.

| Action                  | Parts of Plant | Extract/Compound | Animal Model                          | Dosage | Results                                                                 | References |
|-------------------------|----------------|------------------|---------------------------------------|--------|--------------------------------------------------------------------------|------------|
| **Antidiabetic effects**| Rhizomes       | Methanol         | STZ-induced                           | 50, 100, and 200 mg/kg, p.o. to rats | ↓ Lipid profile and blood glucose, while ↑ levels of plasma insulin, tissue glycogen, and GfPD | [105]      |
|                         | Ethyl acetate  | Alloxan-induced  | Genetically obese diabetic             | 150 and 200 mg/kg, p.o. to rat      | ↓ Levels of triglycerides and serum glucose                               | [106]      |
|                         |                | Genetically obese diabetic |        | 100 mg/kg, p.o.                        | ↑ Secretion of GLP-1 and ↓ blood glucose levels                          | [107]      |
|                         |                | GLP-1 expression and secretion with STZ-induced |       | 100 mg/kg, i.g.                        |                                                                        | [108]      |
|                         | Ethyl acetate  | In vitro HIT-T15 cell line and alpha-glucosidase enzyme | 6.25, 12.5, and 25 µg/mL. | Glucose tolerance | 400 and 800 mg/kg, p.o. to mice | ↑ Secretion of GLP-1 and ↓ blood glucose levels | [109]      |
|                         | Ethanol and aqueous | Ethanol and aqueous | HFD-induced                           | 100 and 200 mg/kg to rats | ↓ Levels of serum cholesterol and triglycerides, ↑ lipoprotein fraction | [110]      |
| **Anti-obesity effects**| Diethyl ether  | HFD-induced      | 20 and 40 mg/kg, p.o. to rats          | ↑ Total cholesterol and low-density lipoprotein levels, ↑ plasma fibrinogen levels | [111]      |
|                         | Methanol       | Triton-X-100-induced hyperlipidemic | 250 and 500 mg/kg to rats | Anti-hyperlipidemic effect | Dose-dependent |
|                         | Aqueous        | HFD-induced      | 100, 200, and 300 mg/kg, p.o. to rats | ↓ Levels of serum glucose, leptin, and insulin along with ↓ triglyceride, low-density lipoprotein, very LDL cholesterol, total cholesterol, phospholipids, and free fatty acid increased levels [SIP and DFP] blood urea nitrogen, creatinine and LPO, ↑ level of nitric oxide, SOD, CAT, GPX | [112]      |
| **Antihypertensive effects** | Ethyl acetate  | Clamping the left kidney artery for 4 h | Blood pressure lowering effect in normotensive | 250 mg/kg, p.o. to rats | Relaxant effects mediated through Ca$^{2+}$ antagonism and NO pathways | [113]      |
|                         | Crude extract, ethyl acetate and n-hexane | Dimethyl sulfoxide-induced noise stress to rats | 10, 30, and 50 mg/kg to anesthetized rats | Destructive effect of stress enlightening the morphological changes of hippocampus | [114]      |
| **Anti-inflammatory effects** | Ethanol and α-asarone | Carrageenan-induced paw edema | 100 and 9 mg/kg, p.o. to rats | Histamine, 5-HT, and kinins | ↑ SOD and LPO, decreased ↑ CAT, GPX, GSH, vitamins C and E, and protein thiol levels | [115]      |
|                         | Leaves         | Ethanol          | 100 and 200 mg/kg to rats             | ↑ Histamine, 5-HT, and kinins      | ↑ SOD and LPO, decreased ↑ CAT, GPX, GSH, vitamins C and E, and protein thiol levels | [116]      |
| **Antioxidant effects** | Rhizomes       | Ethanol          | Noise stress induced to rats          | 3, 6, and 9 mg/kg, i.p. to rats    | Prominent DPH scavenging activity, chelating ferrous ions, reduntingpower | [117]      |
|                         | Leaves and rhizomes | Ethyl acetate and methanol | DPPH radical scavenging activity, chelating ferrous ions, FRAP | 200, 100, 80, 60, 40, 20, 10, and 5 µg/mL. | MDA and ↑ SOD, CAT, GPX, GSH levels | [118]      |
|                         | Rhizomes       | Ethanol          | Acetaminophen-induced                 | 250, 500 mg/kg, p.o. to rats       |                                                                        | [119]      |
| Action               | Parts of Plant | Extract/Compound                  | Animal Model                          | Dosage               | Results                                                                 | References |
|---------------------|----------------|-----------------------------------|---------------------------------------|----------------------|-------------------------------------------------------------------------|------------|
|                     | Roots          | Ethanol and β-asarone             | Kainic acid-induced convulsion        | 35 and 20 mg/kg      | ↓ Epileptic seizure, neuroprotective, and regenerative ability          | [123]      |
|                     | Methanol       |                                   | PTZ-induced convulsion                | 100 and 200 mg/kg, p.o. to mice | ↓ Latency period and ↓ PTZ-induced seizure time                        | [124]      |
|                     | Calamus oil    |                                   | MES, PTZ, and MCS model              | 30, 100, and 300 mg/kg, p.o. to mice | ↓ Hind limb extension and tonic flexion of forelimbs                  | [125]      |
|                     | Ethanol        |                                   | MES and PTZ-induced convulsion       | 250, 500 mg/kg, p.o. to mice | ↓ Immobility time at 250 mg/kg; however, ineffective at 150 mg/kg     | [126]      |
| Anticonvulsant effects | Rhizomes       | Methanol                           | MES and PTZ-induced convulsion       | 250 and 150 mg/kg, p.o. to rats | ↓ Immobility time in a dose-dependent manner                           | [127]      |
|                     | Roots          | Aqueous                            | TST and FST                          | 75 and 150 mg/kg, p.o. to mice | ↓ Immobility time                                                       | [128]      |
|                     | Methanol       |                                   | TST and FST                          | 72 mg/kg, p.o.       | ↓ Corticosteroid levels                                               | [129]      |
|                     | Methanol and acetone | β-asarone                | Behavioral despair test              | 5, 20, and 50 mg/kg, p.o. | ↓ Immobility time                                                       | [130]      |
|                     | Hydro-alcoholic extract |                           | EPM and FST                          | 25, 50, and 100 mg/kg, p.o. | ↓ Immobility time                                                       | [131]      |
| Antidepressant effects | Rhizomes       | Ethanol                            | CCI of sciatic nerve-induced neuropathic pain | 10 mg/kg to rats       | ↓ Spontaneous locomotor activity                                       | [132]      |
|                     | Methanol and acetone |                           | CCI of sciatic nerve-induced peripheral neuropathy | 100 and 200 mg/kg to rats | ↓ Neurally ameliorated CCI-induced nociceptive pain                     | [133]      |
| Neuroprotective effects | Roots          | Methanol                           | Apomorphine-induced stereotypy and haloperidol-induced catalepsy | 20 and 50 mg/kg to mice | Reversed stereotypy induced by apomorphine and significantly potentiated catalepsy induced by haloperidol | [134]      |
|                     | Ethanol        |                                   | Spontaneous electrical activity and monoamine levels of the brain | 200 and 300 mg/ kg to rats | Depressive response by altering electrical activity, including changing brain monoamine levels | [135]      |
|                     | Hydro-alcoholic | MCAo-produced brain ischemia      | Methotrexate-induced stress          | 5, 10, 15, 20, 25 ppm concentration to fruit flies | ↓ Elevated ROS, SOD, CAT, and GPX levels                                | [136]      |
|                     | Ethanol        |                                   |                                         |                      | ↓ Force and rate of contractions at higher concentrations              | [137]      |
| Cardioprotective effects | Whole plant    | DOX-induced myocardial toxicity   |                                         |                      |                                                                         | [138]      |
|                     | Hydro-alcoholic |                                   |                                         |                      |                                                                         | [139]      |
|                     | Ethanol        |                                   |                                         |                      |                                                                         | [140]      |
|                     | Whole plant    | Crude, n-hexane, ethyl acetate    | Guinea pig tracheal segments         | 0.01 mg/mL           |                                                                         | [141]      |
|                     | Rhizomes       |                                   |                                         |                      |                                                                         | [142]      |

CAT, catalase; CCI, chronic constriction injury; COX, cyclooxygenase; DBP, diastolic blood pressure; DOX, doxorubicin; DPPH, 2,2-diphenyl-1-picrylhydrazyl radical; EPM, elevated plus maze; FRAP, ferric reducing antioxidant power; FST, forced swim test; GLP-1, glucagon-like peptide-1; GPX, glutathione peroxidase; GR, glutathione reductase; GSH, reduced glutathione; HDL, high-density lipoproteins; HFD, high-fat diet; HPM, high plus maze; i.e., intragastric; i.p., intraperitoneal; LDL, low-density lipoprotein; LPO, lipid peroxides; MCAo, middle cerebral artery occlusion; MCS, minimal clonic seizure; MDA, malondialdehyde; MES, maximal electroshock; NO, nitric oxide; OBF, open field behavior; p.o., per oral; PTZ, pentylenetetrazol; ROS, reactive oxygen species; SBP, systolic blood pressure; SOD, superoxide dismutase; STZ, streptozotocin; TST, tail suspension test.
6.1. Antidiabetic Effect

The antidiabetic effect of *A. calamus* ethyl acetate fraction was evaluated in streptozotocin (STZ)-induced and diabetic (db/db) mice. Glucagon-like peptide-1 (GLP-1) levels, plasma insulin, “and related gene expression were evaluated. The fraction (100 mg/kg, intragastric (i.g.)) indicated a significant reduction in blood glucose levels. For in vitro, at the concentration of 12.5 µg/mL, a significant increment in GLP-1 levels was found in the insulin-secreting L-cell culture medium [108]. The ethyl acetate radix fraction exhibited a significant effect on the HIT-T15 cell line and α-glucosidase enzyme. The ethyl acetate fraction also enhanced insulin secretion in HIT-T15 cells and blocked the α-glucosidase in vitro activity with 0.41 µg/mL of inhibitory concentration (IC₅₀) [109].”

6.2. Anti-Obesity Effect

The β-asarone compound isolated from the rhizome was investigated against high-fat diet (HFD)-induced obesity in animals. β-Asarone-treated adipose rats showed weight loss, but also inhibited metabolic transformations, as well as glucose intolerance, elevated cholesterol, and adipokine variance [143]. The in vitro investigation on the *A. calamus* aqueous extract showed lipid-lowering activity through inhibition of the pancreatic lipase percentage (28.73%) [144].

6.3. Antihypertensive Effect

The antihypertensive effects of *A. calamus* were studied on their own, in isolation, and in combination with *Gymnema sylvestre* in the HFD-induced hypertension in rats. The HFD was given for 4 weeks, which significantly increased the average systolic blood pressure (SBP). At a 200 mg/kg dose, *A. calamus* in combination with *G. sylvestre* reduced the SBP and heart rate significantly. *A. calamus* with *G. sylvestre* exhibited synergistic effect as compared with individual herbs [145].

6.4. Anti-Inflammatory and Immunomodulatory Effect

The methanolic *A. calamus* rhizome extract (12.5 µg/mL) prevented the VCAP-1 and intercellular expression on the surface of mouse myeloid leukemia cells and murine endothelial cells, respectively [146]. In an in vitro anti-inflammatory study (Red blood cell membrane stabilization method), the *A. calamus* aqueous rhizome extract at the highest concentration of 10 mg/mL showed insignificant activity against hemolysis inhibition and the RBC membrane stabilization percentage [144]. Aqueous *A. calamus* leave extract was studied on HaCaT cells and restricted the characteristics of interleukin (IL)-8, IL-6 RNA protein levels alongside interferon regulatory factor 3 (IRF3) and nuclear factor kB (NF-κB) activation [147]. N-hexane, butanolic, and aqueous fractions of *A. calamus* were evaluated against cyclooxygenase (COX) and lipoxygenase (LOX)-mediated eicosanoid production by arachidonic acid. The butanolic fraction inhibited the COX-mediated production of thromboxane B2 (TXB2) and lipoxygenase product 1 (LP1). Investigation of the underlying signaling pathways revealed that the butanolic fraction inhibited phospholipase C (PLC) pathway in platelets, presumably acting on protein kinase C (PKC) [148]. The essential oil isolated from *A. calamus* was evaluated by protein denaturation assay, where at the concentration level of 300 µg/mL, 69.56% of the inhibition level was observed [149].

6.5. Antioxidant Effect

The in vitro antioxidant activity of acetone, acetonitrile, alcoholic, and aqueous extracts of *A. calamus* rhizomes exhibited free radical scavenging activity on the [2,2′-azinobis (3-ethylbenzothiazoline-6-sulphonic acid)] free radical scavenging activity assay (ABTS), the (1, 1-diphenyl-2-picyrylhydrazyl) free radical scavenging activity assay (DPPH), and the ferric ion reducing antioxidant power assay (FRAP). Strong antioxidant effect was noticed in the acetone extract, followed by acetonitrile and methanol, while in the aqueous extract, poor antioxidant activity was found [150]. The aqueous extract exhibited superior antioxidant effects in metal ion chelation, lipid peroxidation (LPO), and DPPH assays [144,151]. The in vitro antioxidant activity of ethanol, hydro-ethanol, and aqueous whole plant extracts of
A. calamus was investigated using FRAP, DPPH, nitric oxide, hydroxyl radical, reductive ability, and superoxide radical scavenging activity. The existence of phenolics and flavonoids in A. calamus are believed to contribute to the promising antioxidant effect. IC$_{50}$ values of the ethanol extract were found to be 54.82, 109.85, 38.3, 118.80 $µg/mL$ for the scavenging activities of DPPH, hydroxyl radical, superoxide radical, and nitric oxide, respectively. The irreversible potential of the above results and the FRAP values of the extracts were found to augment in a concentration-dependent manner [152]. “Ethanol and hydro-alcoholic extracts of A. calamus roots and rhizomes were studied for antioxidant potential against DPPH compared with butylated hydroxyanisole (BHA) and silymarin. Ethanol and hydro-alcoholic extracts showed free radical scavenging activity of 59.13 $±$ 18.95 and 56.71 $±$ 19.54, respectively [153–155]. The essential oil isolated from A. calamus showed strong antioxidant efficacy against the $β$-carotene/linoleic acid bleaching test and DPPH free radicals [156]. The methanol extract of the A. calamus rhizome was evaluated against the free radical scavenging activity, and the reported IC$_{50}$ value was 704 $µg/mL$ [157]. The IC$_{50}$ of the essential oil was 1.68 $µg/mL$, which showed virtuous free radical scavenging activity in the DPPH test [149].”

6.6. Anticonvulsant Effect

The methanol extract shows anticonvulsant effects feasibly through potentiating the action of gamma-aminobutyric acid (GABA) pathway in the central nervous system [124]. When it comes to the purification of A. calamus rhizome in cow urine, it is advocated in the Ayurvedic pharmacopoeia of India (API) before its therapeutic use. The purified rhizome was investigated in a maximal electroshock (MES) seizure model, and phenytoin was used as the standard drug. The raw and processed rhizome (11 mg/kg, p.o.) exhibited notable anticonvulsant activity by minimizing the span of the tonic extensor period in rats, whereas the processed rhizome showed better therapeutic activity than when it was raw [158]. The calamus oil isolated from the A. calamus rhizome was evaluated at varying dose levels of 30, 100, and 300 mg/kg, p.o., body weight (b.w.), against MES, pentylenetetrazol (PTZ), and minimal clonic seizure (MCS) models. The calamus oil was found to be neurotoxic at 300 mg/kg, though it was effective in the MCS test at 6 Hz. The protective index value of calamus oil was found to be 4.65 [125].

6.7. Antidepressant Effect

Interaction of the methanolic A. calamus rhizome extract with the adrenergic, dopaminergic, serotonergic, and GABAergic system was found responsible for the expression of antidepressant activity [128]. In another study, the methanolic A. calamus leave extract showed significant activity through a reduction in the immobility period in the TST and FST [129]. Through interaction with the adrenergic and dopaminergic system, the hydro-alcoholic extract was normalized to the over-activity of the hypothalamic pituitary adrenal (HPA) axis [131]. Sobers capsules (a herbo-mineral formulation containing A. calamus) were evaluated by tail suspension and forced swimming tests in mice. At the oral dose of 50 mg/kg for 14 days, capsules exhibited insignificant impact on locomotor activity, and caused antidepressant effects in experimental animals [159]. Tensarin (the traditional medicine of Nepal containing A. calamus) was evaluated for the anxiolytic effect in mice using the open field test (OFT), activity monitoring along with the passive avoidance test. At all three dose levels (50, 100, 200 mg/kg), Tensarin produced an anxiolytic effect in a dose-dependent way by an improvement in rearing, number of passages, and duration of the period employed by mice [160].

6.8. Neuroprotective Effect

The ethanolic extract was studied (25, 50, and 100 mg/kg doses, oral and intraperitoneal routes) for learning and memory-enhancing activity. The subjects used consisted of male rates, through Y maze and shuttle box tests models. The findings showed an increase in acquisition–recalling and spatial recognition data [161]. The ethanolic A. calamus rhizome extract (0.5 mL/kg, i.p.) potentiated pentobarbitone-created sleep periods, which caused significant inhibition of conditioned avoidance response in rats and marked (40–60%) protection against PTZ-induced convulsions, although it did
not show any spontaneous motor activity and impact the aggressive or fighting behavior response in male rat pairs [162].

6.9. Cardioprotective Effect

The alcoholic *A. calamus* rhizome extract (100 and 200 mg/kg) considerably attenuated isoproterenol-led cardiomyopathy in rats and showed a significant reduction in the heart/body weight ratio, level of serum calcineurin, serum nitric oxide, serum lactate dehydrogenase (LDH), and thiobarbituric acid reactive substances (TBARS) level. However, the level of the antioxidant enzyme was found increased at the 100 mg/kg extract dose level [163]. The crude extract and its fractions (0.01–10 mg/mL) were investigated in an isolated rabbit heart, which showed mild reduction in the force of forced vital capacity (FVC), hazard ratio (HR), and cystic fibrosis (CF), while the ethyl acetate extract exhibited complete suppression, and the n-hexane fraction showed the same effect on FVC and HR, but enhanced CF. The extract and its fractions exhibited controlled coronary vasodilator effect, interceded maybe by an endothelial-derived hyperpolarizing factor [164]. The cardioprotective potential of the whole plant’s ethanolic extract (100 and 200 mg/kg) reduced serum enzyme levels and shielded the myocardium from the lethal effect of DOX [141].

6.10. Cytochrome Inhibitory Activities

Cytochromes P450 (CYPs) are the prime enzymes that catalyze the oxidative metabolism of a wide variety of xenobiotics. It is known that 2,4,5-trimethoxycinnamic acid is the main metabolite of α- or β-asarone [165]. The metabolism rate of α- and β-asarone was shown to be directly proportional to the CYPs concentration in rat hepatocytes and liver microsomes [166,167]. CYP3A4 (CYP isoforms) has been reported for bioactivation of α-asarone [168]. The hydro-alcoholic *A. calamus* extract and α-asarone were evaluated by the CYPs-carbon monoxide complex method. The extract exhibited moderate potential interaction in CYP3A4 (IC$_{50}$ = 46.84 µg/mL) and CYP2D6 (IC$_{50}$ = 36.81 µg/mL), while α-asarone showed higher interaction in CYP3A4 (IC$_{50}$ = 65.16 µg/mL) and CYP2D6 (IC$_{50}$ = 55.17 µg/mL) [169]. These outcomes indicated that both extracts and α-asarone interacted quite well in drug metabolism and also had an inhibitory effect on CYP3A4 and CYP2D6. The drug-drug interaction effect of the *A. calamus* extract and its main chemical constituent (α and β-asarone) needs to be studied in more CYPs isomers, like CYP2C9 and CYP2E1.

6.11. Toxicity and Safety Concerns

In acute and sub-acute toxicity of the hydro-alcoholic extract of *A. calamus* in rats, at the highest dose level of 10 gm/kg, no severe changes were observed, and the lethal dose (LD$_{50}$) was found to be 5 g/kg [170]. The petroleum ether extracts (obtained by cold rolling, water distillation, and Soxhlet extraction methods) of the *A. calamus* rhizome showed mild toxicity in two-day-old oriental fruit flies [171]. The ethanolic extract of the *A. calamus* rhizome at oral dosage of 175, 550, 1750, and 5000 mg/kg b.w. was given for 14 days within an acute toxicity study, while at the dose level of 0, 200, 400, and 600 mg/kg, p.o., the extract was given for 90 days within a chronic toxicity study. At the doses of 1750 and 5000 mg/kg, piloerection, tremors, and abdominal breathing were found for 30 min [172]. In that study, *A. calamus* was purified for 3 h in cow urine, decoction of *Sphaeranthus indicus*, and decoction of leaves of *Mangifera indica*, *Eugenia jambolana*, *Feronia limonia*, *Citrus medica*, and *Aegle marmelos*, followed by fomentation with Gandhodaka (decoction of six aromatic herbs) for 1 h. The acute oral toxicity test of raw and purified *A. calamus* was performed in albino rats at 2000 mg/kg for 2 weeks. At the 2000 mg/kg dose, *A. calamus* did not produce any toxic symptoms within 14 days [173].

The β-asarone compound isolated from *A. calamus* was found to be carcinogenic and toxic [174]. The LD$_{50}$ value of β-asarone by oral and intraperitoneal route was found to be 1010 and 184 mg/kg, respectively, in mice and rats [175]. The LD$_{50}$ of calamus oil was found to be 8.88 gm/kg b.w. [176], while in the calamus oil obtained from Jammu, India, the LD$_{50}$ was 777 mg/kg b.w. [177]. Overall,
several investigations have been carried out on *A. calamus* regarding its toxicity; however, no noticeable data on toxicity have been found so far.

7. Clinical Reports

*A. calamus* has also been clinically investigated as a monotherapy as well as in combination with other medicinal herbs in healthy subjects and sufferers of various metabolic and neurological ailments. Most clinical research has looked at the *A. calamus* effect on obesity, depression, neuroprotection, and cardiovascular disease [178–191]. The data obtained so far can be found in Table 5. Furthermore, a systematic review reveals that *A. calamus* (alone or in combination therapy) exhibits anti-obesity, antidepressant, and cardioprotective effects, as well as helps physical and mental performance.
Table 5. Clinical claims of *A. calamus* in neurological and metabolic disorders.

| Formulations/Dosage forms | A. calamus | Subjects | Study Design | Intervention | Primary Endpoint | Outcome | Evidence Quality | Reference |
|---------------------------|------------|----------|--------------|--------------|------------------|---------|------------------|-----------|
| A. calamus rhizome powder | 24 patients of both sexes with hyperlipidemia | Randomized single-blind controlled study | 500 mg twice daily after meal for 1 month | BMI, body perimeter, skinfold depth | Significant reduction in skinfold depth, fatigue, and excessive hunger | III | [179] |
| Dauwale Baman capsules (A. calamus, nut grass, incense, ginger, and black pepper) | 24 patients of both sexes with Alzheimer’s disease | Double-blind randomized clinical study | 500 mg capsule thrice daily for 3 months | ADAS-cog and CDR-SOB scores | At 4 weeks and 12 weeks: significant reduction in the ADAS-cog and CDR-SOB scores | III | [179] |
| 70% hydro-alcoholic extract of A. calamus | 33 patients of both sexes (20 male and 13 female) with anxiety disorder | Non-randomized, open-label, single-arm study | 500 mg extract of one capsule twice daily after meal for 2 months | BPRS score | Significant reduction of anxiety and stress-related disorder | III | [180] |
| Vachadi Churna (A. calamus, Cyperus rotundus, Cedrus deodara, ginger, Acorus calamus, C. pluricaulis, T. chebula) | 30 obese patients of both sexes aged 14–50 years | Non-randomized, open-label, single-arm study | 3 g powder twice daily with lukewarm water before meal for 1 month | BMI, girth measurements of mid-thigh, abdomen, hip, chest | Significant improvement in extreme sleep, body heaviness, fatigue, and excessive hunger | III | [181] |
| Gaduchayadi Medhya Rasayana, (A. calamus, Tinospora cordifolia, Achyranthes aspera, Embelia ribes, Costus beatus, T. chebula, S. lappa, Asparagus racemosus, cow ghee, and sugar) | 138 patients of both sexes aged 55–75 years with senile memory impairment | Randomized, two-parallel-group study | 3 g granule thrice daily after meal for 3 months | Mini-Mental State Examination, BPRS score, and estimation of serum acetylcholinesterase | Significant improvement in terms of recall memory, cognitive impairment, amnesia, concentration ability, depression, and stress | III | [182] |
| Dried aqueous extract of A. calamus | 40 healthy volunteers, both sexes aged 18–50 years with a premedicant for anaesthesia | Randomized single-blind controlled study | 60 min before anesthesia, In the control group: 0.2 mg intramuscular (IM) glycopyrrolate and a 0.2 mg IM 50 mg tablet of promethazine hydrochloride with water, In the second group: 0.2 mg IM glycopyrrolate and 100 mg A. calamus extract | Pulse rate, blood pressure, respiratory rate, body temperature | The dried aqueous extract exhibited anti-hyperthermic and sedative effect without producing any respiratory depression | III | [183] |
| Shankhapushpyadi Ghana Vati (A. calamus, C. pluricaulis, Bacopa monnieri, T. cordifolia, C. fistata, A. indica, S. lappa, Tribulus terrestris) | 20 hypertensive patients of both sexes | Randomized single-blind controlled study | 1 g twice daily after meal for 2 months | SBP and DBP | Significant relief in raised SBP and DBP | III | [184] |
| Brahmyadiyoga (A. calamus, Centella asiatica, Rauwolfia serpentina, Saussurea lappa, Nardostachys jatamansi) | 10 schizophrenic patients of both sexes aged 18–40 years | Non-randomized, open-label, single-arm study | 4 tablets thrice daily for three months after meal | Symptoms rating scale | Significant effect as a brain tonic, tranquilizer, hypnotic, and sedative | III | [185] |
| Bala compound (A. calamus, Emblica officinalis, E. ribes, T. cordifolia, Piper longum, Glycyrrhiza glabra, C. notandus, A. heterophyllum) | 24 neonates, both sexes, 2.5–3 kg body weight | Randomized single-blind controlled study | 5 oral drops twice daily for 6 months | Change in serum immunoglobulins (IgG, IgM, and IgA) levels | Significant improvement in immunoglobulin levels after 6 months | lb | [186] |
| Vachadi Churia (A. calamus, T. cordifolia, Hedychium spicatum, C. pluricaulis, E. ribes, ginger, A. aspera, T. chebula, and cow ghee) | 90 healthy individuals of both sexes aged 40–50 years for assessment of cognition | Non-randomized positive-controlled study | 10 g twice daily for 1 month with lukewarm water | Post Graduate Institute Memory Scale (PGIMS) test | Significant change in the mental balance score, holding of like and different pairs, late-immediate memory, and also improved digestion | III | [187] |
### Table 5. Cont.

| Formulations/Dosage forms | Subjects | Study Design | Intervention | Primary Endpoint | Outcome | Evidence Quality | Reference |
|---------------------------|----------|--------------|--------------|------------------|---------|------------------|-----------|
| Bramhi Vati (A. calamus, B. monnieri, C. plancus, O. tincti, copper pyrite, iron pyrite, mersicur sulphide, Piper nigrum, N. jatamansi) | 68 essential hypertension patients of both sexes aged 20-70 years | Randomized, double-blind, parallel-group comparative study | 500 mg tablets twice daily for 1 month | Hamilton anxiety rating scale, SBP and DBP, and MAP | Significant improvement in the Hamilton anxiety rating scale, SBP and DBP, and MAP | III | [188] |
| Tagaradi Yoga (A. calamus, Valeriana wallichii, N. jatamansi) | 24 insomnia patients of both sexes aged 18-75 years | Non-randomized positive-controlled study | 500 mg hydro-alcoholic extract capsule twice daily after meal for 15 days | Sleep duration, initiating time of sleep, quality of sleep | Significant improvement in sleep duration, in the initiating time of sleep, and in quality of sleep | III | [189] |
| Acorus calamus rhizome powder | 20 obese patients of both sexes | Randomized single-blind study | 250 mg rhizome powder twice daily for 1 month | Body weight, height according to age, waist-hip ratio, and BMI | Significant improvement in extreme sleep, body heaviness, fatigue, and excessive hunger | III | [190] |
| Acorus calamus rhizome powder | 45 ischemic heart disease patients | Non-randomized positive-controlled study | 3 gm rhizome powder twice daily for 3 months | ECG, serum cholesterol level | Improvement of chest pain, dyspnea on effort, reduction of the body mass index, improved ECG; reduced serum cholesterol, reduced serum LDL, and increased serum HDL | lb | [191] |

ADAS-cog, alzheimer’s disease assessment scale–cognitive subscale; BMI, body mass index; BPRS, brief psychiatric rating scale; CDR-SOB, clinical dementia rating scale sum of boxes; DBP, diastolic blood pressure; ECG, electrocardiogram; Ig, immunoglobulin; III, evidence from well-performed nonexperimental descriptive studies, as well as from comparative studies, correlation studies, and case studies; LDL, low-density lipoprotein; MAP, mean arterial pressure; SBP, systolic blood pressure.
8. Mechanistic Role

The proposed mechanism of action of *A. calamus* in neurological and metabolic disorders includes a synergic integration of antioxidant defense, GABAergic transmission, brain stress hormones modulation, pro-inflammatory cytokines, leptin and resistin levels, adipocytes inhibition, calcium channel blocker effect, protein synthesis, oxidative stress, acetylcholinesterase (AChE) inhibition, and anti-dopaminergic properties. A compendium of mechanisms of action of *A. calamus* in neurological and metabolic protection is illustrated in Figure 6 and Table 6. *A. calamus* significantly affects fasting blood sugar, insulin resistance, HbA1c, and the adipogenic transcription expression factor through various mechanisms, viz. antioxidant, anti-inflammatory, β-cells regeneration, improving insulin sensitivity, gluconeogenesis, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, and glucose transporter type 4 (GLUT-4)-mediated transport inhibition.

**Figure 6.** Illustration of role of *A. calamus* mechanisms in the treatment of neurological and metabolic disorders. AcE, acetylcholinesterase; APP, amyloid precursor protein; Bcl-2, B-cell lymphoma 2; CHOP, C/EBP homologous protein; CCAAT (cytosine-cytosine-adenosine-thymidine)-enhancer-binding protein homologous protein; C/EBP, CCAAT enhancer-binding protein; GABAA, γ-Aminobutyric acid type A; GRP78, 78-kDa glucose-regulated protein; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; iNOS, inducible nitric oxide synthase; JNK, c-Jun NH2-terminal kinase; LC3b, microtubule-associated proteins 1A/1B light chain 3B; MCP, modified citrus pectin; MDA, malondialdehyde; MIP, macrophage inflammatory protein; p-PERK, phospho-protein kinase RNA-like ER kinase; PPARγ, peroxisome proliferator-activated receptor gamma; ERK1/2, extracellular signal-regulated protein kinase.
Table 6. Mechanistic role of phytochemicals of *A. calamus* in the treatment of neurological and metabolic disorders.

| Study | Compound | Model | Increased Level | Decreased Level | References |
|-------|----------|-------|-----------------|-----------------|------------|
| Anti-Parkinson | 6-OHDA parkinsonian | Bcl-2 expression | GRP78, p-PERK, CHOP, and Beclin-1 expression | | [192] |
| | 6-OHDA parkinsonian | - | mRNA levels of GRP78 and CHOP and p-IRE1 and XBP1 | | [193] |
| | Dopamine in the striatum | TH plasma concentrations | Striatal COMT levels | | [194] |
| | 6-OHDA parkinsonian | L-DOPA, DA, DOPAC, and HVA levels | P-gp, ZO-1, occludin, actin, and claudin-5 | | [195] |
| | Aβ25-35-induced inflammation | Bcl-2 level | TNF-α, IL-1β, IL-6, Beclin-1, and LC3B level | | [196] |
| | NG108 cells | - | Upregulated SYP and Glur1 expression | | [197] |
| | PC12 cells | - | Aβ-induced JNK activation, Bcl-w and Bcl-xL levels, cytochrome c release, and caspase-3 activation | | [198] |
| | Aβ-induced cytotoxicity | Cell viability, p-Akt and p-mTOR | NSE levels, Beclin-1 expression | | [199] |
| | Pb-induced impairments | NR2B protein expression along with Arc/Arg3.1 and Wnt7a mRNA levels | - | | [200] |
| Neuroprotective | β-Asarone, eugenol | Scopolamine-induced | Improvement of neuron organelles and synaptic structure | APP expression | [201] |
| | Neotatarine | MTT reduction assay | - | Aβ25-35–induced PC12 cell death | [202] |
| | β-asarone, paenol | MCAo model | Cholecystokinin and NF-κB signaling | TNF-α, IL-1β, IL-6 production | [203] |
| Study | Compound | Model | Increased Level | Decreased Level | References |
|-------|----------|-------|-----------------|----------------|------------|
| Neuroprotective | β-Asarone | Cultured rat astrocytes | NGF, BDNF, and GDNF expression | - | [204] |
| | | SN4741 cells | p62, Bcl-2 expression | JNK, p-JNK and Beclin-1 expressions | [205] |
| | Tatarinolactone | hSERT-HEK293 cell line | - | SERTs activity | [206] |
| | | RSC96 Schwann cells | GDNF, BDNF, and CNTF expression | - | [207] |
| | | Aβ-induced | p-mTOR and p62 expression | AChE and Aβ42 levels, p-Akt, Beclin-1, and LC3B expression, APP mRNA and Beclin-1 mRNA levels | [208] |
| | | Aβ1–42-induced injury | - | GFAP, AQP4, IL-1β, and TNF-α expression | [209] |
| Anti-depression | α-Asarone | Noradrenergic and serotonergic neuromodulators in TST | α1 and α2 adrenoceptors and 5-HT1A receptors | - | [211] |
| | | Chronic unpredictable mild stress | BDNF expression | Blocked ERK1/2-CREB signaling | [210] |
| Anticonvulsant and sedative | Eudesmin | MES and PTZ | GABA contents, expressions of GAD65, GABA-A, and Bcl-2 | Glu contents and ratio of Glu/GABA, caspase-3 | [212] |
| Anti-anxiety | α-Asarone | BLA or CFA-induced | Down-regulation of GABA_A receptors | Up-regulation of GluR1-containing AMPA, NMDA receptors | [213] |
| Anti-epilepsy | α-Asarone | Temporal lobe epilepsy | Levels of GABA, GAD67, and GABAAR-mRNA expression | GABA-T | [214] |
| | | Mitral cells | Down-regulation of GABA_A receptors | Na+ channel blockade | [215] |
| | β-Asarone | KA-induced | GABA | Glu | [216] |
Table 6. Cont.

| Study                  | Compound               | Model                          | Increased Level                                             | Decreased Level                                             | References |
|------------------------|------------------------|-------------------------------|-------------------------------------------------------------|-------------------------------------------------------------|------------|
| Anti-inflammatory      | α-Asarone              | Spinal cord injury            | IL-4, IL-10, and arginase 1 levels                          | TNF-α, IL-1β, IL-6, MCP-1, MIP-2, iNOS levels              | [217]      |
| Cytoprotective         | β-Asarone              | tBHP-induced astrocyte injury | GST, GCLM, GCLC, NQO1, Akt phosphorylation                  | -                                                          | [218]      |
| Cardioprotective       |                        | Cultured neonate rat cardiac myocytes | Viability of cardiac myocytes                              | Pulse frequency                                             | [219]      |
| Arteriosclerosis       | β-Asarone              | ECV304 cell strain            | Apoptotic rate of ECV304 cells                              | Apoptotic rate of MMP, stabilized MMP and VSMC proliferation | [220]      |
| Anti-adipogenic        |                        | 3T3-L1 preadipocytes          | -                                                          | C/EBPβ, C/EBPα, and PPARγ expression levels, ERK1/2 phosphorylation | [89]       |
| Antioxidant            |                        | Cerebral artery occlusion     | Antioxidant activity                                        | Focal cerebral ischemic/reperfusion injury                  | [221]      |
| Anti-diabetic          | α-Asarone + β-asarone + metformin HCl | STZ-induced Insulin level | Glucose, glycosylated hemoglobin level, liver dysfunction, and tumor biomarkers | Intracellular triglyceride levels, down-regulation of PPARγ and C/EBPα | [222]      |
| Asarone                |                        | 3T3-L1 preadipocytes          | Hormone-sensitive lipase phosphorylation                   | -                                                          | [223]      |

6-OHDA, 6-hydroxydopamine; Ox-LDL, oxidized low-density lipoprotein; BDNF, brain-derived neurotrophic factor; NGF, nerve growth factor; CDNF, glial derived neurotrophic factor; SERTs, serotonin transporters; MCAo, middle cerebral artery occlusion; Aβ, β-amyloid; NSE, neuron specific enolase; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; NMAD, NR2A-containing N-methyl-D-aspartate; GABA_A, γ-aminobutyric acid A; BLA, basolateral amygdala; CFA, complete Freund's adjuvant; CNTF, ciliary neurotrophic factor; COMT, catechol-O-methyltransferase; TH, tyrosine hydroxylase; DA, dopamine; DOPAC, 3,4-dihydroxyphenylacetic acid; HVA, homovanillic acid; P-gp, P-glycoprotein; ZO-1, zonula occludens-1; SYP, synaptophysin; GluR1, glutamatergic receptor 1; GABA-T, GABA transaminase; TST, tail suspension test; KA, kainic acid; MCP-1, monocyte chemoattractant protein 1; iNOS, inducible nitric oxide synthase; GST, glutathione S-transferase; GCLM, glutamate-cysteine ligase catalytic subunit; VSMC, vascular smooth muscle cells; MMP, mitochondrial membrane potential; C/EBP, CCAAT enhancer-binding protein; PPARγ, peroxisome proliferator-activated receptor gamma; ERK1/2, extracellular signal-regulated protein kinase; XBP1, x-box binding protein; IRE1, inositol-requiring enzyme 1; Aβ1-42, amyloid β peptide; mTOR, mammalian target of rapamycin; MTPT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide; CREB, cAMP response element-binding protein; GABAAR, gamma-aminobutyric acid type-A receptor; tBHP, t-butyl hydroperoxide.
The antihypertensive effect of *A. calamus* may be explained by Ca$^{2+}$ antagonists that affect the nitric oxide pathway. The chemical constituents of *A. calamus* upregulate the antioxidant effect, suppress pro-inflammatory cytokines, and act as detoxifying enzymes through the NF-κB and nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathways. The Nrf2 pathway may be activated by phenylpropanoids, sesquiterpenoids, and monoterpenes by interaction of active phytoconstituents with nitric oxide derivatives react with thiol groups between KEAP1 and Nrf2, along with Nrf2 phosphorylation. “When Nrf2 is released from the Kelch-like erythroid-derived CNC (cap’n’collar) homology protein (ECH)-associated protein 1 (KEAP1), it transfers into the nucleus, where it induces the genes encoding protein expression impenetrable in glutathione (GSH) synthesis, antioxidant, and detoxifying phase 2 enzymes. Oxidative stress and ligands for tumor necrosis factor receptors (TNFRs) and toll-like receptors (TLRs) activate upstream Ik-B kinases (IKKs), ensuing phosphorylation of IkB that is generally bound to the inactive NF-kB dimer in the cytoplasm. After that, IkB is targeted for proteasomal degradation and NF-kB, then it moves into the nucleus where it induces inflammatory cytokine expression in addition to the genes encoding proteins like superoxide dismutase (SOD) 2 and B cell chronic lymphocytic leukemia (CLL)/lymphoma 2 (Bcl2) involved in adaptive stress response (Figure 7). The bioactive molecules of *A. calamus* can inhibit NF-kB in inflammatory immune cells, while other phytoconstituents may activate NF-kB in neuronal cells to improve stress resistance.” *A. calamus* phytoconstituents regulate NF-kB, LOX, and COX-2 activity. These compounds dose-dependently suppress the production of inflammatory factors like NO, TNF-α, IL-6, IL-1β, and JNK signaling, acting as anti-inflammatory agents. In addition, it was also noted that the inflammation induced by various chemicals was inhibited by bioactive constituents through suppression of IkB/NF-kB and JNK/AP-1 signaling pathways. Thus, over several studies, it has been reported that asarone compounds have a potential against neurodegenerative diseases.

PPAR gene and C/EBP are involved in the differentiation process. PPAR-δ and PPAR-γ promote adipogenesis. In the same way, amino acids and glucose react with C/EBP-δ and C/EBP-β. If low levels of glucose induce gadd153, the inactive dimer is formed, with C/EBP-β inhibiting the progress of adipocyte development. C/EBP delta activates C/EBP-α. This is mainly involved in the formation of mature adipocytes and lipid accumulation in adipose tissue. In 3T3-L1 preadipocytes, α-asarone and β-asarone inhibited adipocyte differentiation and reduced the intracellular lipid accumulation, and also decreased the expression levels of adipogenic transcription factors (PPARγ and C/EBPα). These phytochemicals significantly promoted adenosine monophosphate-activated protein kinase (AMPK), which is known to suppress adipogenesis. It was also found that pretreatment with α-asarone and β-asarone, a typical inhibitor of AMPK, attenuated the inhibitory effect of asarone on AMPK phosphorylation. The asarone-induced AMPK activation leads to a decrease in adipogenic transcription factor expression, and suppresses adipogenesis.
4. Ethnomedicinal Use

This plant is being practiced traditionally in the Indian Ayurvedic tradition, as well as in the Chinese system of medicine for analgesic, antipyretic, tonic, anti-obesity, and healing purposes; it is highly effective for skin diseases, along with neurological, gastrointestinal, respiratory, and several other health disorders. Rhizomes and leaves are found to be profusely practiced in the form of infusion, powder, paste, or decoction [13–72]. The ethnomedicinal uses of the *A. calamus* are detailed in Table 1. *A. calamus* rhizomes and leaves are also used as an active pharmaceutical ingredient in various Ayurvedic formulations (Table 2).

9. Perspectives and Future Directions

The present review provides a plethora of information apropos ethnomedicinal uses, marketed formulations, geographical distribution, chemical constituents, pharmacological activities of crude, n-hexane, ethyl acetate, methanolic, ethanolic, hydro-alcoholic, aqueous extracts along with pure compounds, and clinical trials related to *A. calamus*. Investigations on extracts and compounds of *A. calamus* suggested antidiabetic, anti-obesity, antihypertensive, anti-inflammatory, antioxidant, anticonvulsant, antidepressant, neuroprotective, and cardioprotective potentials with distinct underlying signaling pathways. The biological potential and mechanisms of action of some of the chemical constituents (α-asarone, β-asarone, eugenol) are known. However, other compounds need to be scientifically explored for their bioactivities and molecular modes of action, which could provide a lead for further development into therapeutics. More systematic, well-designed, and multi-center clinical studies are warranted to evaluate standardized extracts of *A. calamus* therapeutically and to identify the pharmacokinetic-dynamic roles of pharmacologically active biomolecules. There is scarce data from experimental and clinical reports on hypertension, diabetes, and atherosclerosis, and less supporting evidence is available on the use of *A. calamus* to treat hypertension and diabetes. Based on the available data, it is suggested that this plant could be used as an adjuvant to the established targeted drugs for neurological and metabolic disorders.

In 1974, United States food & drug administration (USFDA) banned *A. calamus* due to its carcinogenic effects following animal studies. They reported β-asarone as a carcinogenic agent, but the study was conducted on the calamus oil which consists of β-asarone in about 80%, while its different genotype in Europe and India contains β-asarone in lower concentrations. *A. calamus* cultivated...
in various geographical regions may have different chemical compositions along with therapeutic properties challenging quality control, toxicity, and safety concerns of *A. calamus*. In addition, the heavy metal, mycotoxin, and pesticide concentrations are required to be addressed in all toxicity studies.

10. Conclusions

Compelling in vitro, in vivo and clinical evidence suggests that the potential role of *A. calamus* rhizomes for modulating metabolic and neurological disorders could be due to their richness in several classes of active phytoconstituents. The predominant compounds present in rhizomes and leaves responsible for expression of potent bioactivities include α-asarone, β-asarone, eugenol, and calamine. The present report is expected to fill the gaps in the existing knowledge and could provide a lead for researchers working in the areas of phytomedicine, ethnopharmacology, and clinical research.

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