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Alkamides: Multifunctional Bioactive Agents in *Spilanthes* spp.

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Abstract: **Plant bioactives have always been a source of many valuable medicines. Alkamides are a class of pseudoalkalloidbioactives that are distributed among 33 medicinal plant families including Asteraceae (Compositeae). Genus *Spilanthes*ofAsteraceae family is a storehouse of various potent alkamides. Spilanthol is considered as a key compound with its maximum concentration in the flower heads. Alkamides are pungent in taste and show analgesic and anaesthetic properties. These have been reported to exhibit significant larvicidal/insecticidal, antimicrobial, aphrodisiac, antimutagenic, anti-inflammatory and immune-enhancing pharmacological activities. Also, transdermal and transmucosalbehaviour of spilanthol has been well documented. Therefore, alkamide content make this genus a promising medicinal plant with several biological and pharmacological activities. Thus, this review presents an overview of different alkamides in *Spilanthes* with an emphasis on their properties, distribution, pharmacological aspects and mode of administration.**

Index Terms: **Alkamide, Anti-inflammatory, Asteraceae, Bioactive, Insecticidal, Spilanthol.**

I. Introduction

Medicinal plants have been a source of powerful bioactive agents since time immemorial virtually in all cultures and have provided valuable drugs such as analgesics (morphine), antitussives (codeine), antihypertensives (reserpine), cardiotonics (digoxin), antineoplastics (vinblastine and taxol) and antimalarials (quinine and artemisinin) (Ramawat*et al*., 2009). There are about 2, 50,000 higher plant species on the earth, out of which more than 80,000 are found to possess medicinal value. But due to the lack of proper documentation and scientific validation only a small proportion of the plants are used for their medicinal values (Balunas&Kinghorn, 2005). However, the recent past has witnessed a tremendous revival of interest in the use of medicinal plant products due to the various drawbacks associated with synthetic medicines. Hence, there is a need to review the valuable knowledge regarding medicinal plants with proper investigation of bioactive compounds and their properties.

Plant bioactives are the secondary products of primary metabolism representing an important source of active pharmaceuticals. These have been defined as chemicals that do not appear to have a vital biochemical role in the process of building and maintaining plant cells but apparently function as defence (against herbivores, microbes, viruses or competing plants) and signal compounds (to attract pollinating or seed dispersing animals) (Beran*et al*., 2019; Briskin, 2000; Kaufman *et al*., 1999; Wink &Schimmer, 1999). Such secondary products involved in plant defence through cytotoxicity towards microbial and insect pathogens could prove useful as antimicrobials and insecticidals for human benefits (Benelli*et al*., 2018).

One highly promising class of secondary compounds i.e ‘Alkamides’ form active constituent of many plant families. Genus *Spilanthes*(Asteraceae)popularly known as Toothache Plant has been found as a storehouse of alkamides. Out of 60 species of the genus scattered all over the tropical areas of the globe (Jansen, 1981), six species *S. acmella*Murr. (syn. *Acmellaciliata*), *S. acmella* L. var. *oleraceae*(syn. *Acmellaoleraceae*L.), *S. calva* L., *S. paniculata* and *S. mauritiana* L. have been accounted from Chhattisgarh (Tiwari*et al*., 2011), Jharkhand (CSIR, 1989) and Rajasthan regions (Sharma *et al*., 2010) of India. The genus *Spilanthes* has been reported to possess erect or prostrate stems, triangular, dentate and opposite leaves. Flowers grow solitary with long peduncle and have yellow florets with dark red spot in the centre (Tiwari*et al*., 2011).

Out of the severalphytochemicalsreported from *Spilanthes*, alkamides have been considered to be responsible for most of its medicinal properties so far. Presently, alkamide containing extracts of *Spilanthes* are commercially sold as dietary supplements, powerful antiseptics **(**Dentaforcemouthspray&

mouthwash, VogelSpilanthes tincture) (Silveira*et al.*, 2018), analgesics (Herbaluna*Spilanthes* tincture) and antivirals (*Spilanthes* supreme-by Gaia Herbs) by a number of herbal extract manufacturers. Moreover, it has been used as a flavouring agent in carbonated beverages, for improving the taste of sweeteners of high sweetness (Delacina*et al*., 2007; Gregar, 2015; Miyazava*et al*., 2006) and in anti-wrinkle cosmetic preparations (Ada, 2007; Belfer, 2007; Dias, 2012; Schubnel, 2007). Due to its wide application, isolation of alkamide constituents and investigation of their pharmacological activity has become an important subject of research. The present review highlights the distribution, types, properties, and available preparations of the alkamides with emphasis on genus *Spilanthes*.

II. Alkamides And Their Distribution

Amides build up by the condensation of carboxylic acids and amines with the elimination of a water molecule. Similarly, alkamides are produced by the condensation of an unsaturated fatty acid with an amine (Hofer *et al*., 1986), thereby, known as fatty acid amides. Plant alkamides are classified as protoalkaloids or pseudoalkaloids (Rios, 2012) because the nitrogen atom of alkamides is not part of a heterocyclic ring.

Out of the 33 plant familiesalkamides are abundantly found in the Aristolochiaceae, Rutaceae, Piperaceae andAsteraceae families (Boonen*et al*., 2012; Greger& Werner, 1990; Rios &Olivo, 2014). *Acmella*, *Anacyclus*, *Artemisia*, *Echinaceae*, *Heliopsis*, *Spilanthes*, *Salmea*, *Sanvitalia*and *Wedelia*are major alkamide-producing genera of the Asteraceae family that are known to possess the capacity to combine C8 to C18 (with exception of C17) olefinic and acetylenic acid residues with the more widespread *N*-isobutyl, *N*-2-methylbutyl, *N*-phenethyl and cyclic amines like piperidinyl (piperidide), 2, 3-dehydro-piperidinyl (piperideide), pyrrolidinyl and pyrrolidyl (Saraf&Dixit, 2002; Rios, 2012). Although the biogenetic route of N-alkylamides has not yet been clarified, it was proposed that these compounds were biosynthesized from fatty acids and amino acids in the Asteraceae family (Rios &Olivo, 2014).

III. Distribution Of Alkamides In *Spilanthes*

Several alkamides, predominantly isobutylamides have been documented in several species of *Spilanthes*including: *S. oppositifolia, S. acmella, S. mauritiana, S. alba, S. americana,S. radicans, S. ocymifolia, S. ciliata,* and *S. calva.* Concentration of alkamides varies between different species, different parts as well as different developmental stages of the plant. A study on the spilanthol concentration in flowering heads, leaves, roots and stems of *Spilanthesacmella*Murr. at different growth and developmental stages revealed the maximum content in flowering heads (in bud capitulum stage -4.84%), followed by root (in two month old plants -1.39%), shoot (in both one month and two month old plants -1.25%) and least in leaves (in young stage - 0.61%) (Nayak& Chand, 2002).

The genus*Spilanthes*mostly possesses aliphatic amides such as isobutylamide which is a subclass of alkamides. The core isobutylamide in the genus *Spilanthes* is Spilanthol or affinin. Spilanthol is 2E, 6Z, 8E-N-isobutylamide 2, 6, 8-decatrienamide with chemical formula $C_{14}H_{23}NO$ and molecular weight of 221.2 (Yasuda *et al*., 1980). The namespilanthol was given by Gerber (1903) to the pungent principle from *S. oleraceae.* Isolation of pure spilanthol from the flower heads of *S. acmella* was first reported by Asano & Kanematsu (1927). Then, Gokhle&Bhide (1945) also obtained it from the aerial parts of *S. acmella*. In a study, flower head extract of *S. acmella* has been reported to be comprised of 50% spilanthol, 10% a weaker pungent compound N-(2-methylbutyl)-2, 6, 8- decatrienamide isomer and the rest of 40% is acetylenicalkamide N-isobutyl-2-nonene-6, 8-diynamide and its phenylethyl derivatives (Nakatani&Nagashima, 1992). A further report on simultaneous distillation-solvent extraction (SDE) and supercritical fluid (CO_2) extraction (SFE) studies of *S. americana* showed that SFE extracts from leaves and flowers were abundant in nitrogenated (43 and 27%) and oxygenated (36 and 23%) compounds like (isobutyl)-2*E*,6*Z*,8*E*-decatrienamide, N-(2-methylbutyl)-2*E*,6*Z*,8*E*-decatrienamide, N-(isobutyl)-6*Z*,83-decadienamide and N-(2-phenelethyl)2-*E*,6*Z*,-8*E*-decatrienamide but only trace-level contents of nitrogenated compounds were found in SDE extracts (Stashenko*et al*., 1996). A HPLC/ESI-MS method was proposed for quantitative and qualitative analysis of spilanthol in plant samples (Bae*et al*., 2010).Thereafter, an efficient one step quantitative isolation technique Centrifugal Partition Chromatography has been reported for isolation of alkamides in *S. acmella* (Mbeunkui*et al*., 2011). One more report showed major presence of spilanthol in *S. oleracerea* L. (Rios, 2012). This finding is supported by one more study on *N*-alkylamide profiling using a gradient reversed phase high performance liquid chromatography/electrospray ionization ion trap mass spectrometry (HPLC/ESI-MS) method on an embedded polar column which has confirmed spilanthol (88.84%) as a major alkamide and 2-methylbutylamide (9.04%), the second most abundant alkamide in ethanolic flower extractof *S. acmella*(Boonen*et al*., 2012). Later, using the liquid/liquid partition procedure of the ethanolic extract obtained from dried leaves of *Acmellaoleracea*two new alkamides deca-6,9-dihydroxy-(2*E*,7*E*)-dienoic acid isobutylamide, deca-8,9-dihydroxy-(2*E*,6*Z*)-dienoic acid isobutylamide were isolated (Simas*et al*.,2013). Recently a bioassay-guided separation of the *S. paniculata*ethanolic extract led to the isolation of a new allkamide (2E,7Z)-6,9-endoperoxy-N-2-methylbutyl-2,7-decadienamide. (Abdjul*et al.*, 2018).Various alkamides reported in *Spilanthes* are presented in the table 1and structures detected from NMR and MS studies of different alkamides are presented in Fig. 1.

IV. General Properties Of Alkamides

Alkamides including spilanthol has a strong, pungent taste and produce local astringency and anaesthetic effects. Spilanthol is a pale yellow liquid with boiling point 220-225^{0}C (20mm) and absorption in UV at 220mµ (Aihara, 1950; Jacobson,1956). Alkamide compounds produce tingling sensation in mouth (Ramsewak*et al*., 1999). Besides, these are chemically and physiologically somewhat related to the sanshools found in Sichuan pepper (Saraf&Dixit, 2002). It has been shown that fatty acid part of alkamides strongly influences its sensorial action (Ley *et al*., 2004). The tingling effect may be mediated by different ion-channel receptors on different types of sensory neurons, like the capsaicin (transient receptor potential vanilloid type 1 (TRPV1)), TRPA1, TRPM8 receptor, while more recently, emphasis is placed on distinct receptors like KCNK3, KCNK 9 and KCNK 18 (two-pore potassium channels) (Bautista *et al*., 2008; Sharma *et al*., 2011).

V. Pharmacological Aspects Of Alkamides

*Spilanthes*has been used conventionally by the tribes to treat toothaches, stammering, stomatitis, paralysis of tongue, asthma and rheumatism. *Spilanthes* extract containing alkamides has been reported to exhibit significant analgesic, larvicidal/insecticidal, antimicrobial, anti-inflammatory, vasorelaxant, immunomodulatory, aphrodisiac and antimutagenic properties.

Spilanthol is the prime larvicidal compound found in *Spilanthes*. Ethanolic extract of *S. acmella* is one by ten part active in comparison to DDT against larvae (Pendse*et al*., 1946). The methanolic extract of *S. mauritiana* having *N*-isobutyl-2*E*,4*E*,8E,10*Z*-dodeca-2,4,8,10-tetraenamide is also a potent mosquito larvicide causing 100% mortality against the larvae of *Aedesaegypti* at 10^{-5} mg/ml (Jondiko, 1980). In a study, spilanthol from *S. acmella* extracts was found to be 1.3, 2.6 and 3.8 times more toxic than carbaryl, bioresmethrin and lindane, respectively against adults of American cockroach where it inhibited the cercal nerve activity (Kadir*et al*., 1989).12.75 µg/ml of Spilanthol cause 100% mortality of *Aedes* larvae (Ramsewak*et al*., 1999). Similar study with purified spilanthol proved 4-7.5 ppm concentration deleterious to the various larval stages of *Anopheles, Culex and Aedes* mosquito. Spilanthol actually disturbs the nerve conduction in larvae and interrupts the processes of histolysis and histogenesis (Saraf&Dixit, 2002). Another study has reported an increase in the mortality of *A. gambiae* and *C. quinquefasciatus* with the increase in concentration and time of exposure to methanolic extracts of S. *mauritiana* (Ohago*et al*., 2007). Moreover, it has been found that mixture of alkylamides produces a significantly higher antiplasmodial activity as compared to purified alkylamides, which might be possible due to interactions between these alkylamides (Mbeunkui, 2011). A mixture of active alkamides consisting of nona-2Z-en-6,8-diynoic and deca-2Z-en-6,8-diynoic acid phenethylamide from *Acmellaoleraceae* was shown to be active against *A. aegypti* larvae at LC50 = 7.6 ppm (Simas*et al*., 2013). Such profound larvicidal /insecticidal activity has accredited the genus with immense potential to be developed as an effective antimalarial agent.

Antibacterial property of *Spilanthes* extract is shown against 12 strains of *Helicobacter pylori* (Fabry*et al*., 1996). In another report *S. americana*did not showed inhibition against C.*albicans*but*S. mauritiana* (roots and flowers) showed MIC and MBC values > or = 8 mg/ml against *Staphylococcus*, *Enterococcus*, *Pseudomonas*, *Escherichia*, *Klebsiella*, *Salmonella* (Fabry*et al*., 1998). It has been also reported that the antifungal potential of *S. calva* can be increased by inoculation of endophyte*Piriformosporaindica* (Rai*et al*., 2004). In addition, spilanthol is proved to be one of the active components for the treatment of microbial infections especially against oral pathogenic microorganisms (Adler, 2006; Dias *et al*., 2012). About 2000µg of *S. acmella* flower head extract produced highest inhibition zone of 2.3cm in*Fusariumoxysporium*followed by2.1 cm in*Fusariummoniliformis*, 2.0cm in*Aspergillusniger,* 1.8 cm in*Aspergillusparaciticus*(Sabitha&Suryanarayana, 2006). In a study, root extract of *S. calva* showed 54.54%, 50%, 63.63% inhibition of *S. mutans*, *L. acidophilus* and *C. albicans* respectively which is comparable to the inhibitions produced by herbal dentrifice (Arodent) and synthetic dentrifice (Colgate) *in vitro* using human tooth model.Also, The crude extracts of *S. oleracea* showed highly potent antimicrobial activity against a population of isolated pathogenic oral organisms(Onoriode&Oshomoh, 2018*)*.

Spilanthol has also been reported to show anti-inflammatory activity by efficiently down-regulating the production of pro-inflammatory mediators (IL-1, IL-6, and TNF-R), expression of cyclooxygenase 2 and inducible nitric oxide synthases enzymes which are the key components of the inflammatory pathway that can also be inhibited by the reduced activation of transcription factor nuclear factor-κB. Spilanthol acts by competitively inhibiting cyclooxygenase and 5-lipoxygenase as well (Muller-Jakie*et al*., 1994; Dias*et al*., 2012). In an another study enzyme-linked immunosorbent assay revealed a reductionin the release of Interleukin-8 and Tumor NecrosisFactor - alpha by leukocytes exposed to spilanthol (Blanco *et al*., 2018).

Furthermore, Spilanthol is involved in immunostimulatory activity (Wu *et al*., 2008) due to its structural relatedness with sphingolipids such as ceramide and sphingosine (Ng & Hetherington, 2001; Ramırez-Chavez *et al*., 2004).

Also, profound analgesic activity has been reported(Dandin*et al*., 2014; Paulraj*et al*., 2013; Prachayasittukal*et al*., 2013).

Additionally Spilanthol has been reported to show antimutagenic potential. Nitrosation of methylurea leads to the formation of the direct acting mutagen, N- nitrosomethylurea. Alkamide compounds like Spilanthol have the ability to restrain mutagenesis by nitrosating themselves to non-mutagenic products instead of methylurea thus reducing the yield of nitrosomethylurea (Sukumaran&Kuttan, 1995). Also, the spilanthol is reported to reduce 2AA- and NOR-induced mutations inTA98 and TA102 strains of *Salmonella typhimurium* (Arriaga-Alba *et al*., 2013).

It has also shown to possess aphrodisiac properties due to the ability to take off the action of testosterone or stimulate secretion of testosterone and inducible Nitric Oxide activity which enhances the erectile response leading to improved sexual behaviour in male rats (Sharma *et al*., 2011).

Moreover, alkamides structurally resembles N-Acylethanolamines (Lopez *et al*., 2007) which play signaling role in important biological functions in plants such as germination (Teaster*et al*., 2007; Wang *et al*., 2006), defense responses (Chapman *et al*., 1998) and root development (Blancaflor*et al*., 2003; Lopez *et al*., 2007). A study revealed affinin (*Heliopsis*- alkamide same as that of spilanthol) to alter the growth and development of the *Arabidopsis* root system (Ramı´rez-Cha´vez*et al*., 2004). Therefore, spilanthol is expected to exhibit plant growth regulating properties as well as enhancing the plant biomass production (Campos-Cuevas, *et al*., 2008; Rios, 2012).

VI. Alkamides And Their Administration

Mode of administration of any drug/therapeutic plant active depends upon its pharmacokinetic activity. The intrinsic local pharmacokinetics study of spilanthol following topical application on human skin has established its permeability through skin (Boonen*et al*., 2010a). This has confirmed its topical use in fungal and bacterial infections. A transmucosal mode of application has also been reported where rich microcirculation with direct drainage of blood into the internal jugular vein permits systemic effects of permeated alkamide molecules through buccal mucosa (Boonen *et al*., 2010 b;Squier, 1991). Moreover, it has also been reported to cross blood-brain barrier after entering into systemic circulation (Veryser*et al*., 2014).

VII. Alkamides And Their Marketed Products

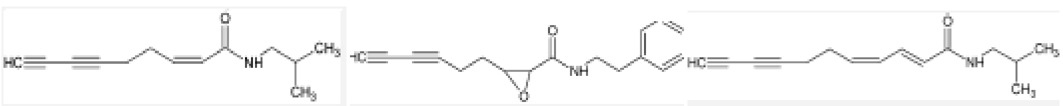
Several preparations of the spilanthol are available in the market like: Oral gels- Buccaldol® from Alphamega, France and Indolphar® from ID Phar, Belgium (Silviera, 2018), Mouthwash-Dentaforcemouthspray and mouthwash, Antiseptic tincture- Vogel spilanthes tincture containing 65% ethanol from Biohorma, Belgium), Anti- wrinkle cream- (Demarne&Passaro, 2009) and Anti-aging products- Gatuline®, SYN®-COLL, ChroNOline™ (Veryser*et al*., 2014).

Table I: Detectedalkamides in *Spilanthes*

Spilanthesspp.	Extraction technique	Compound	References
S. acmella	Gradient reverse phase HPLC-ESI-MS	Spilanthol	Ramsewaket al., 1999
	HPLC-MS	Undeca–2E,7Z,9E–trienoic acid isobutylamide, Undeca–2E–en-8,10-diyonic acid isobutylamide, 2E–N-(2-methylbutyl) –2–undecene–8,10–diynamide, 2E,7Z–N-isobutyl–2,7-tridecadiene–10,12–diynamide, 7Z-N-isobutyl-7-tridecene-10,12-diynamide	Nakatani and Nagashima, 1992
	HPLC-UV, ESI-MS-MS	(2E,4E,8Z,10E)-N-isobutyl-2,4,8,10-dodecatetraenamide	Sharma et al., 2011
	HPLC-UV, ESI-MS-MS	(2E,7Z)-N-isobutyl-2,7-decadienamide, Homospilanthol, N-phenethyl-2,3-epoxy-6,8-nondiynamide, (2Z)-N-isobutyl-2-nonene-6,8-diynamide, (2E,4Z)-N-isobutyl-2,4-undecadiene-8,10-diynamide	Boonenet al., 2010
S. alba	1H and 13C NMR, MS, GC-MS	Spilanthol	Ramsewaket al., 1999
	HPLC-MS	Undeca–2E,7Z,9E–trienoic acid isobutylamide, Undeca–2E–en-8,10-diyonic acid isobutylamide	Nakatani and Nagashima, 1992
	DN	(2E,4E,8Z,10E)-N-isobutyl-2,4,8,10-dodecatetraenamide	Molina et al., 1996
S. ciliata	DN	spilanthol, 2,3-dihydro derivatives of spilanthol	Martin and Becker 1984
S. oppositifolia	DN	Spilanthol, N 2-methyl butyl-deca 2E,6Z,8E-trienamide	Molina et al., 1996
S. oleracea	VCC, GC-1H- and 13C-NMR	(2E,4E,8Z,10E)-N-isobutyl-2,4,8,10-dodecatetraenamide	Phrutivorpungaletal.,2008
	HPLC-MS	2E–N-(2-methylbutyl) –2–undecene–8,10–diynamide,	Nakatani and

		2E,7Z–N-isobutyl–2,7-tridecadiene–10,12–diynamide, 7Z-N-isobutyl-7-tridecene-10,12-diynamide	Nagashima, 1992
S. ocymifolia	DN	N-2-Phenylethylcinnamamide	Borges-Del-Castillo, 1984
S. americana(Mutis) Hieron.	Simultaneous SDE, SFE	Nitrogenated (N-(isobutyl)-2E,6Z,8E-decatrienamide, N-(isobutyl)-6Z,8E-decadienamide, N-(2-phenelethyl)2-E,6Z,-8Edecatrienamide), N-(2-methylbutyl)-2*E*,6*Z*,8*E*-decatrienamide	Stashenkoet al., 1996
S. radicans	GC-MS	N-isobutyl-(2E,6Z,8E)-decatrienamide, N-(2-methylbutyl)-(2E,6Z,8E)-decatrienamide, N-(2-phenylethyl)- (2Z,4E)-octadienamide, N-(2-phenylethyl)-nona-2E-en-6,8-diynamide, N-(2-methylbutyl)(2E,4Z,8E,10E)dodecatetraenamide, 3-phenyl-N-(2-phenylethyl)-2- propenamide	Rios-Chavez et al., 2003
Acmellaoleracea	Liquid/liquid partition	deca-6,9-dihydroxy-(2*E*,7*E*)-dienoic acid isobutylamide, deca-8,9-dihydroxy-(2*E*,6*Z*)-dienoic acid isobutylamide	Siman et al., 2013

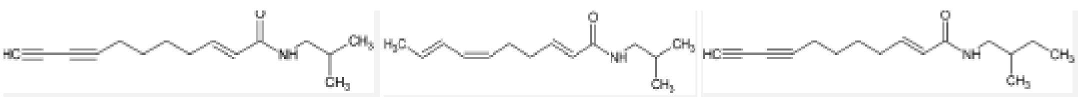
HPLC-High Pressure Liquid Chromatography, ESI-Electrospray Ionisation, MS-Massspectrometry, GC-Gas Chromatography, VCC-Vaccum Column Chromatography, NMR-Nuclear magnetic Resonance, SFE-Supercritical Fluid Extraction, DN-Data not found



(2*Z*)-*N*-isobutyl-2-nonene-6,8-diynamide[c]

N-phenethyl-2,3-epoxy-6,8-nonadiynamide[c]

(2*E*,4*Z*)-*N*-isobutyl 2,4-undecadiene-8,10-diynamide[c]



(2*E*)-*N*-isobutyl-2-undecene-8,10-diynamide[c]

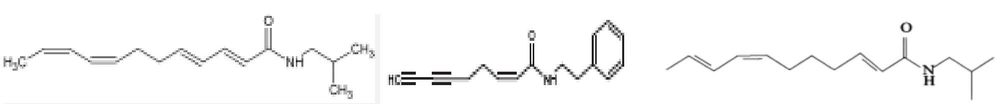
(2*E*,6*Z*,8*E*)-*N*-isobutyl-2,6,8-decatrienamide[c]

(2*E*)-*N*-(2-methylbutyl)-2-undecene-8,10-diynamide[c]

(2*E*,7*Z*)-*N*-isobutyl-2,7-tridecadiene-10,12-diynamide[c]

(2*E*,7*Z*)-*N*-isobutyl-2,7-decadienamide[d]

(2*E*,6*Z*,8*E*)-*N*-(2-methylbutyl)-2,6,8-decatrienamide[c]



(2*E*,4*E*,8*Z*,10*Z*)-*N*-isobutyl-dodeca-2,4,8,10-tetraenamide[c]

(2Z)-N-phenethyl-2-nonene-6,8-

Undeca-2E,7Z,9E-trienoic acid isobutylamide

Fig. 1. Structure of various alkamides detected in *Spilanthes* sp. (from Boonen*et al*., 2010)

CONCLUSION

Alkamides are a group of promising secondary metabolites, lipophilic in nature. These have been detected in many plant genera namely *Acmella*, *Anacyclus*, *Artemisia*, *Echinaceae*, *Heliopsis*, *Spilanthes*, *Salmea*, *Sanvitalia*and *Wedelia*. The mainstream interest in *Spilanthes* is only recently fuelled by pre- clinical test results which are mainly attributed to its principal therapeutic isobutylamide compound spilanthol. Different species of *Spilanthes* including *S. acmella*, *S. acmella* L. var. *oleraceae*, *S. calva* L., *S. paniculata*, S. *mauritiana*, *S. cilliata*, *S. ocymifolia*, *S. oppositifolia*, *S. alba*,*S.americana*, *S. radicans*have been found to possess this bioactive. Other alkamides like N-(2-methylbutyl)-2, 6, 8- decatrienamide, N-isobutyl-2-nonene-6, 8-diynamide, (2E, 4E, 8Z, 10E)-N-isobutyl-2, 4, 8, 10-dodecatetraenamide, etc (Table I) have been found in *Spilanthes* spp. Whole plant shows the presence of spilanthol with maximum concentration in flower heads followed by roots stems and leaves. LC-MS ESI, supercritical fluid extraction, liquid/Liquid partition techniques have been developed for accurate identification and estimation of spilanthol. This has been reported to exhibit significant larvicidal/insecticidal, antimicrobial, aphrodisiac, antimutagenic, anti-inflammatory, immune-enhancing activities. Moreover, transdermal and transmucosal properties of spilanthol can be an effective mode of its local and systemic administration respectively. Therefore, multipurpose medicinal applications make alkamides of spilanthes a potent multifunctional drug.

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