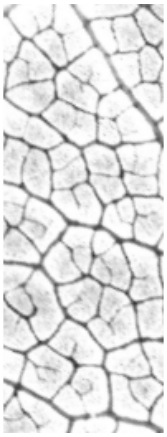

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Anti-inflammatory activity of extracts of selected West African ethnomedicinal plants

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Abstract
The adverse effects of currently use anti-inflammatory drugs have constituted a lots of health hazards after their usage. Herbal medicines from plants with documented and long cultural use against inflammation can be of great significance hence plants choice in this study. The medicinal plants are used in this study are employed traditionally to manage pains at the body joints, arthritis, for wound healing and rheumatism. The *in vitro* anti-inflammatory property of methanol extracts of twenty-two (22) plants were evaluated in terms of the nuclear factor kappa B (NF-κB), specific protein 1 (Sp-1) and inhibition of inducible nitric oxide synthase (iNOS). Parthenolide was used as standard. Most extracts showed anti-inflammatory activity through inhibition of iNOS, the most remarkable amongst these are: methanolic extracts of *D. metel, C. papaya, M. lucida* and *T. gleucescens* which exhibit activity with IC50 (µg/mL) values of 1.8, 17, 20 and 23, others like *J. tanjorensis, J. tanjorensis* and *A. wilkesiana* displayed an inhibition with IC50 (µg/mL) value range of 25 – 27. At the concentration of 100 µg/mL; *D. metel*, *C. procera,* and *P. nigresceus* exhibit activity with IC50 (µg/mL) values of 5.8, 41 and 107 respectively when assayed against NF-Kb. Several methanolic extracts employed in this research showed inhibition of iNOS activity indicating their anti-inflammatory effect mediated through decreasing nitric oxide level. This affords some support i.e. scientific evidences to the traditional uses of these medicinal plants against inflammation. This is a back-ground work on the bioassay-guided isolation of anti-inflammatory agents from selected plants, further work is on-going on the isolation of these agents.

Keywords: Nf-Kb, iNOS, anti-inflammatory, *D. metel*, NSAID

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INTRODUCTION

The word inflammation is having its root from the latin "inflammare" to burn (Talat 2007). The biological reaction that occurs in living tissues when there is an injury caused by some dangerous impetuses, irritations caused by soreness, bulging and pain is inflammation and it comprises complex, systemic and local responses (Mohammed et al. 2011). Inflammation can either be acute or chronic inflammation (Ferrero-Millani et al. 2007). Body's primary response to dangerous external or internal stimuli or pain is acute inflammation but when the response to body damage or pain is out of proportion this can be called chronic inflammation (Palladino et al. 2003). In acute and chronic inflammatory disorders enzymes act as mediators (Bemstein et al. 1994, Surh et al. 2001). It has been discovered that cyclooxygenase (COX), nitric oxide synthase (iNOS), 5-lipoxygenase (5-LOX), 12-lipoxygenase (12-LOX), matrix metallo proteinases (MMPs) and hyaluronidases are the normal intermediates in this activity (Hertel *et al.,* 2006). Most of these enzymes release some substances such as human neutrophil elastase (HNE), leukotriene and prostaglandin, these release coupled with the neutrophil stimulation in a range of irritations and very reactive-based human diseases (Manyatepek and Hoffmann 1995). Moreover, the blocking of these enzymes might

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explain the putative antiphlogistic activity of extracts used in managing some of these ailments as recommended by traditionally medicine.

In the earliest time, it was recorded that one of the ways to manage inflammation and pain was the use of medicinal plants, an obvious example is the application of extracts from leaves of willow by Celsius in 30 AD. Acetyl salicylic acid was discovered from its use which is the active compound in aspirin. Medicinal plants with long history of use against pain and arthritis in Western medicine from earliest times, are *Arnica montana* L. (Asteraceae), *Glycyrrhiza glabra* (Fabaceae), *Matricaria chamomilla* L. and *Salix alba* (Salicaceae). Since decades treating inflammation and pain with extracts from willow leaves by Celcius in 30 AD (Yuan *et al*., 2006). Acetyl salicylic acid is a major drug widely employed against inflammation in clinical practice, along with many other non-steroidal anti-inflammatory drugs (NSAIDs), which are current in use (Hougee 2008). NSAIDs drugs are popular in the treatment of pain and inflammatory conditions such as rheumatoid Alzheimer's disease, arthritis and osteoporosis. However, most of the NSAIDs have adverse side effects such as bleeding of the intestine and immune system functions repressed (Hodzic et al. 2009) because of this, medicinal plants were given renewed interest (Buhrmann et al. 2011, Conforti et al. 2008).

In developing countries, most rural dwellers depend on medicinal plants in the treatment of pain and inflammation related diseases. The use of medicinal plants in folklore remedies has become important in the treatment of inflammatory disorders (Matthew et al. 2013). The search for new anti-inflammatory agents from nature i.e. (medicinal plants) is growing since they can form a permeant replacement to the chemically synthetic inflammatory which may also be of immerse benefit by suppressing relevant aspects of the inflammatory cascade. This study therefore, intend to assess and evaluate the anti-inflammatory activity of methanol extracts of plants used in ethno-pharmacological using appropriate assays to authenticate the traditional claims.

MATERIALS AND METHODS

Chemical and Reagents

The reagents and solvents employed in this study are of analytical grade.

Collection and Extraction of Plant Materials

These medicinal plants were collected based on their ethno-biological importance as shown in **Table 1**, Twenty-two (22) plants species belonging to different (19) families were collected (different plant parts) and air-dried between April-October 2015 from Ilorin metropolis, Nigeria. Identification was done by a taxonomic botanist of the department of Botany, University of Ilorin, voucher specimens were deposited. Extraction and evaporation of the extracts of these plants were done according to Bello et al. (2018). Although, it was only the methanol fraction of each plant that was used.

Inhibition of iNOS Activity

This activity was carried out according to methods and procedures reported by some authors (Al-Taweel et al. 2015, Zhao et al. 2014).

Inhibition of NF-kB Activity

The assay was performed on human chondrosarcoma (SW1353, obtained from ATCC) cells as described by methods and procedures as described by some authors (Al-Taweel et al. 2015, Zhao et al. 2014).

Reference Drugs

For the different assays, Parthenolide considered appropriate as reference positive control, this drug was obtained from the manufacturer.

RESULT AND DISCUSSION

The methanolic extracts of twenty-two (22) medicinal plants which belong to 16 families were screened through cellular assays for their anti-inflammatory potential. The methanol fraction for each of the medicinal plant were evaluated for *in vitro* activity in terms of the nuclear factor kappa B (NF-κB), specific protein 1 (Sp-1) and inhibition of inducible nitric oxide synthase (iNOS), the results are expressed in terms of IC_{50} values (the concentration that caused a 50% inhibition) and presented in **Table 2**.

The effect of methanolic extracts on the transcriptional activity of NF-κB was determined in PMA induced human chondrosarcoma (SW1353) cells through a reporter gene assay (Ma *et al*., 2007). From **Table 2**, the twenty-two methanol extracts of the plants were assayed to inhibit NF-κB activity at the concentration of 100 µg/mL, though most extracts didn't exhibit any anti-inflammatory inhibition after the assay has been performed. Methanolic extracts of *C. procera, D. metel* and *P. nigresceus* exhibit potency with IC_{50} (µg/mL) values of 41, 5.8 and 107. Methanolic extract of *D. metel* exhibits a remarkable inhibition with IC_{50} (µg/mL) value of 5.8 while *C. procera* which displayed a weak inhibition. **Table 2** shows that all of the methanolic extracts of the medicinal plants do not possess anti-inflammatory activity through specific protein 1 (Sp-1) inhibition. None of the plants' extracts were active except Methanolic extract of *D. metel* which displayed a weak activity with IC_{50} (µg/mL) value of 70.

The iNOS inhibitory assay was performed in LPS-induced mouse macrophages (RAW264.7) where the concentration of (NO) was determined by measuring the level of nitrite in the cell culture supernatant using Griess reagent (Quang et al. 2006). Most extracts showed inhibition of iNOS potential indicating their anti-

Table 1. Showing Ethnomedicinal Potential of the Plants Used for this Study

	Names and parts used	Family name	English name	Local name	Parts used Traditionally	Ethnopharmacological Uses	References
1	*Vitex grandifolia* Gurke .(Leaves)	Verbenaceae	Black plum	Oriri (Yoruba), Orabin (Igbo)	Bark and leaves	colic, infections of the umbilical cord, toothache, rheumatism, and orchitis	Epidi and Odili (2009), Mbang et al. (2010)
2	*Ceratotheca sesamoides* Endl. *(*Leaves)	Pedaliaceae	Bungu	Eku (Yoruba)	Leaves and Roots	diarrheal, malaria, diabetic milletus, tumour and inflammatory	Adegoke (1968), Fasakin (2004), Irvine (1969), Yakubu et al. (2012), Zeven and de Wet (1982)
3	*Launeae taraxacifolia* (Willd.) Amin ex C. Jeffrey (Leaves)	Asteraceae	Wild Lettuce	Yarin (Yoruba)	Roots and Leaves	whooping cough, pain, wound healing and bronchitis	Ayensu (1978), Ruffina et al. (2016), Sakpere and Aremu (2008)
4	*Jatropha. gossypyfolia* L. (Leaves)	Euphorbiacea	Belly ache bush	Lapalapa (Yoruba)	Leaves	Rheumatism, eye diseases, and bathing wounds	Morton (1968), Ogundare (2007), Stone (1970)
5	*Hymenocardia acida* Tul.(whole plant)	Euphorbiaceae	Heart-fruit	yawa satoje (Fulani), ikalaga (Igbo), and Orunpa (Yoruba)	Bark and Leaves	fever, jaundice, muscular pains, diarrhoea, dysentery and sexual incapacity in males	Abu and Uchendu (2011), Ibrahim et al. (2007)
6	*Jatropha tanjorensis* J. L. Ellis & Saroja (Leaves*)*	Euphorbiacea	'hospital too far', catholic vegetable	Iyana-Ipaja	Leaves	jaundice, diarrheal, stomachache and cough	Duke (1998)
7	*Bryophyllum pinnatum* (Lam.) Oken (Leaves)	Crassulaceae	air plant, miracle leaf, life plant	Odaa-opue (Igbo); ewe abamoda or odundun (Yoruba)	Roots and Leaves	rheumatoid arthritis, tummy bug, injuries from falls, numbness of limbs, bruise, bum and ulcer	Chun-Lin and Rong (2004), Ghasi et al. (2011)
8	*Ocimum tenuiflorum* L. *also known as Ocimum sanctum L (Leaves)*	Lamiaceae	holy basil	Efinrin(Yoruba), Nchuawun(Ibo)	Leaves	common colds, headaches, stomach disorders, inflammation and heart disease	Biswa and Biswa (2005), Jane (2016)
9	*Trichilia monadelpha* (Thonn.) J.J.de Wilde (Leaves)	Meliaceae	NA	ako rere/rere	bark and leaves	pain, psychoses, arthritis, rheumatism, epilepsy, and inflammation.	Abbiw (1990), Dokosi (1998), Lemmens (2008), Odugbemi and Odunayo (2008)
10	*Parquetina nigresceus* (Afzel.) (roots)	Asclepiadaceae/ Periplocaceae	NA	NA	Roots, Leaves and Stem	rheumatism, rickets and asthma	Adeyemi (1994), Imaga et al. (2008), Iwu (1993), Odetola et al. (2006)
11	*Jatropha curcas* L. (Leaves)	Euphorbiacea	Barbados nut/Black vomit nu/Curcas bean	lapa lapa	Roots and Leaves	Skin diseases, joints pain and rheumatism	Blench (2003, 2007), Okujagu et al. (2006), Verma and Gaur (2009)
12	*Datura metel* L. (Leaves)	Solanaceae	Thorn-apple, Devil trumpet	Apikan, Bobo awodi (Yoruba), Nyaranmuo (Ibo).	Leaves and Roots	Swellings and rheumatism, rheumatic pains, hemorrhoids, painful menstruation, skin ulcers and wounds	Anozie (1986), Dabur et al. (2004), Gbile (1980)
13	*Morinda lucida* Benth. (Leaves)	Rubiaceae	Brimstone tree	Nfia(Igbo) Oruwo (Yoruba)	Stem and Leaves	purgative, emetic and diuretic, wounds and joints pain.	Adeneye et al. (2008), Dalziel (1936), Gill (1992), Nweze (2011)
14	*Securinega virosa* (Roxb. ex Willd.) Baill. (stems and leaves)	Euphorbiaceae	Bushweed	ìranjé (Yoruba), tsuwawun karee (Hausa), njisi nta (igbo)	Roots and Leaves	malaria, pneumonia, diarrhea, body pain, stomachache, rheumatism, diarrhea, pneumonia	Dalziel (1936), Magaji (2007b), Neuwinger (1996)
15	*Phyllantus amarus* L. (Leaves)	Euphorbiaceae	Sleeping plant	Iyin Olobe (Yoruba)	Bark and leaves	is used in the treatment of kidney/gallstones, other kidney related problems, appendix inflammation and prostate problems	Adjahloun and Ake assi (1972), Sen and Batra (2013), Ushie (2013)
16	*Ficus exasperate* Vahl. (Leaves)	Moraceae	Sand paper tree/plant	Ewe Ipin (Yoruba)	Leaves and Roots	Ringworm, boils, common anti-ulcer remedy	Adebayo et al. (2009), Gbile et al. (1993), Okoli et al. (2007)
17	*Carica papaya* L. (Leaves and stem)	Caricaceae	Pawpaw	okwulu bekee (Igbo), Ibepe (Yoruba) and kawuse (Hausa)	Leaf, root, fruit and seed	. Its fresh leaves are also efficacious in the treatment of gonorrhea, syphilis and amoebic dysentery	Chinoy et al. (1997), Gill (1992), Odu et al. (2006), Olagunju et al. (2009), Oyekunle and Omope (2010)
18	*Gossypium barbadense* L. (Leaves)	Malvaceae	Cottonseed	Owu (Yoruba)	Leaves	Colds, bronchitis, wounds, systematic diarrheas and pains	Busari (1998), Burkill (1985), Percy and Wendel (1990)
19	*Acalypha wilkesiana* Müll. Arg (Leaves)	Euphorbiaceae	Painted Copper Leaf/ Copperleaf	(Hausa) "Jiwene" and "Jinwinini", (Yoruba) "aworoso	Roots and Leaves	gastrointestinal disorders, swelling and pains, joints pain, fungal skin infections, hypertension	Christman (2004), Forcados et al. (2016), Gilman (1999)
20	*Terminalia gleucescens* Planch. ex Benth. (Leaves*)*	Combretaceae		Idi-apata (Yoruba) Báúshe (Hausa)	Root, and Bark, Leaves	Tooth pain, diabetes mellitus and rheumatism.	Adebayo and Ishola (2009), Lem et al. (2014)
21	*Nymhaea* L. *(Leaves and stem)*	Nymphaeaceae	Water-lily	NA	Stem and leaves	Fever, skin diseases, cancer, pain and wound, gonorrhoea and bronchitis	Akinjogunla et al. (2009), Burkill (1997), Saleem et al. (2001)
22	*Calotropis procera* (Aiton) Dryand *(leaves)*	Asclepiadaceae	Apple of Sodom, Sodom's milkweed, Sodom apple	Bombom (Yoruba)	Leaves, Latex and Stem	Fevers, rheumatism, indigestion, cold, eczema and diarrohea.	Gallegos-Olea et al. (2006), Kew (1985), Morcelle et al. (2004), Ramos et al. (2007)

NA=Not available, Hausa, Yoruba and Igbo are the major languages spoken where the plants are taken

Table 2. Anti-inflammatory Activities of Methanol Extracts of Twenty-Two Ethnomedicinal Plants

S/N	Sample	NF-kB (IC_{50})	SP-1 (IC_{50})	iNOS (IC_{50})	% cell death at the highest conc (100 µg/mL)
1	MeOH of *J. gossypyfolia*	NA	NA	NA	
2	MeOH of *C. procera*	41	NA	NA	
3	MeOH of *Nymphaea*	NA	NA	>100	
4	MeOH of *T. gleucescens*	NA	NA	23	63.89
5	MeOH of *A. wilkesiana*	NA	NA	27	
6	MeOH of *G. barbadense*	NA	NA	100	
7	MeOH of *C. papaya*	NA	NA	17	
8	MeOH of *F. exasperata*	NA	NA	NA	
9	MeOH of *P. amarus*	NA	NA	NA	37.63
10	MeOH of *S. virosa*	NA	NA	90	35.38
11	MeOH of *M. lucida*	NA	NA	20	77.23
12	MeOH of *D. metel*	5.8	70	1.8	86.34
13	MeOH of *J. curcas*	NA	NA	42	
14	MeOH of *P. nigresceus*	107	NA	60	
15	MeOH of *T. monadelpha*	NA	NA	>100	
16	MeOH of *O. tenuiflorum*	NA	NA	27	
17	MeOH of *B. pinnatum*	NA	NA	42	
18	MeOH of *J. tanjorensis*	NA	NA	25	
19	MeOH of *H. acida*	NA	NA	72	
20	MeOH of *V grandifolia*	NA	NA	NA	
21	MeOH of *C. sesamoides*	NA	NA	42	
22	MeOH of *L. taraxacifolia*	NA	NA	37	
23	Parthenolide	0.9	6.5	0.18	
24	Parthenolide	0.6	8	0.15	

inflammatory effect mediated through decreasing nitric oxide level. The most remarkable amongst these are: methanol extracts of *C. papaya, D. metel, M. lucida* and *T. gleucescens* which exhibit activity with IC_{50} (µg/mL) values of 17, 1.8, 20 and 23, others like *J. tanjorensis, J. tanjorensis* and *A. wilkesiana* displayed an inhibition with IC_{50} (µg/mL) value in the range of 25 – 27. The least anti-inflammatory activity was displayed by *G. barbadense, S. virosa* and *P. nigresceus* with IC_{50} (µg/mL) values 100, 90 and 60 while methanol extracts of *J. curcas, B. pinnatum*, *C. sesamoides* and *L. taraxacifolia* displayed a moderate inhibition with IC_{50} (µg/mL) values 42, 42, 42 and 37. It is noteworthy that most extracts showed inhibition of iNOS activity indicating their anti-inflammatory effect mediated through decreasing nitric oxide level. Methanolic extract of *D. metel* exhibit luciferase enzyme activity, it is only this extract that exhibit activity against Sp-1 assay which was used as a control transcription factor which is unresponsive to inflammatory mediators (such as PMA).

History has much record about the medicinal and health purposes of medicinal plants, and their uses in managing diseases and health issues is still well disseminated around the world (Parasuraman et al. 2014). Flavonoids, iridiods and saponins which are well known compounds in medicinal plants do display anti-inflammatory activity through by many mechanisms (Francis et al. 2002, Romano et al. 2013) alongside some other pharmacological effects such as analgesic, anticancer, antidiabetic, antimicrobial, antioxidant, antiplatelet and antiviral activities (Xiao et al. 2014). Extracts from many medicinal plants exert anti-inflammatory action, they are also capable of playing healing role on chronic conditions such as pains in the bones and wound healing that conventional therapeutic treatment may not be able to handle. This study shows the anti-inflammatory activity of some methanolic extracts of these plants especially *D. metel* and *C. papaya*, it will be daunting guess to attribute this observed activity to a single chemical entity. Many of these plants, are tropical plants which contain a broad of various constituents (e.g. alkaloids, carotenoids, flavonoids, phenolics, tannins and saponins etc.) and proteolytic enzymes (chymopapain and papain). Many secondary metabolites found in *papaya* and *datura* (not limited to these two) have been reported to ease the conditions associated with chronic inflammatory and the related side-effects by changing the stages of inflammatory markers (Duke 2015). Rajesh et al. (2013) reported the anti-inflammatory potential of aqueous and methanolic extracts of the leaves of *D. metel*, the activity was established by HRBC membrane stabilization while ascorbic acid was used as the standard (Rajesh et al. 2013). This study confirmed the anti-inflammatory properties of methanolic extracts of some selected medicinal plants mostly *D. metel* and *C. papaya* through inhibition of iNOS activity indicating their anti-inflammatory effect mediated through decreasing nitric oxide level.

Bing-You et al. (2014) reported the isolation of five withanolides from the leaves of *D. metel* L., with four new ones and a known compound. These constituents have been recognized as the main bioactive compounds responsible for inhibitory influences of NO production in LPS-activated macrophage cell line, RAW 264.7 murine macrophages in the extract of the leaves of *D. metel* (Bing-You et al. 2014). Furthermore, Bing-You *et al.,* 2014 isolated nine new withanolides, named daturafolisides A–I, along with six known compounds (22R)- 27-hydroxy-7a-methoxy-1-oxowitha-3,5,24-trienolide-27-O-b-D-glucopyranoside, daturataturin A, daturametelin J, daturataurin B, baimantuoluoside B, 12-

deoxywithastramonolide were identified from *D. metel* L's leaves. These compounds were evaluated for *in vitro* anti-inflammatory potential using LPS-stimulated RAW 264.7 murine macrophages. All these compounds were among them, compounds daturafoliside A, daturafoliside B, baimantuoluoside B and 12-deoxywithastramonolide displayed significant inhibition of nitrite production with values of IC_{50} at 20.9, 17.7, 17.8, and 18.4 µM. These studies highlight the anti-inflammatory action of leaves of *D. metel* which give support to the activity of this plant reported in this study.

Based on traditionally usage, many authors have reported the anti-inflammatory effects of the dried leaves of *C. papaya* (Anibijuwon and Udeze 2009, Owoyele 2008, Rakhimov 2000). Chymopapain, a major constituent of leaves extract of *Carica papaya* was approved in both types of patients who had not responded to conservative therapy and those with documented herniated lumbar intervertebral discs using intradiscal injection in the early 1980s (Sujit et al. 2010). This compound has been in use earlier in surgical wounds recovery and healing (Okeniyi et al. 2007). Papain, another closely related compound to Chymopapain, isolated from leaves of *C. papaya* displayed the ability to maintain active cells while eradicating old tissues (Ravdin 1995). A mixture of papain, urea and ointment with varying percentage was reportedly valuable in healing derided necrotic tissue and liquefy slough in a variety of both short–and long–term lesions ulcers (Burns et al. 1997, Verma et al. 2006). This study complements earlier studies of the anti-inflammatory action of *C. papaya* leaves' extracts.

Despite the evidences from literature of the anti-inflammatory effect (in acute and chronic inflammation) of *Trichilia monadelpha* (Ainooson et al. 2012, Okon et al. 2013), this showed a few deviations from our study. This may be as the result of the leaves extracts of *T. monadelpha* used in this work whereas extracts from stembark were used to justify the ethnomedicinal anti-inflammation of the plant. Limonoids are been reputed to be responsible for the anti-inflammatory activity in the stembark extract of this medicinal plant (Okon et al. 2013).

Among these extracts, our findings are in consonance with those previously reported by without anti-inflammatory activity amongst these are: *Phyllantus amarus, Jatropha gossypyfolia, Calotropis procera, Ficus exasperate, Vitex grandifolia* and *Launeae taraxacifolia* (Abbiw 1990, Adebayo et al. 2009, Ayensu 1978, Dokosi 1998, Epidi and Odili 2009, Gallegos-Olea et al. 2006, Gbile et al. 1993, Kew 1985, Lemmens 2008, Mbang et al. 2010, Morcelle et al. 2004, Morton 1968, Odugbemi and Odunayo 2008, Ogundare 2007, Okoli et al. 2007, Ramos et al. 2007, Ruffina et al. 2016, Sakpere and Aremu 2008, Stone 1970).

FUTURE DIRECTIONS

From this study, the iNOS inhibition of some of the plants' extracts give significant result, likely next phase of this study could be, the Q-PCR experiments may be used to confirm the outcome of these active plants on the transcription of many important pro-inflammatory cytokines such as TNF-α and COX-2. Investigations will be made to know whether these plants' extracts also impede other transcription factors concerned in inflammatory action such as AP-1, STATs and NFI-L6. Future studies would be carried out using various spectroscopy techniques to know and determine the active constituents in the active extracts of some of the medicinal plants. Determination of the specific receptors these active plants' extracts might be acting on to elicit anti-inflammatory effects. There should be *in vivo* evaluation which will involve some small mammals i.e. mice and rats, to validate the anti-inflammatory of these constituents in living systems. In this study, the plants' extracts of *D. metel* and *C. papaya* has a notable activity i.e. inflammatory response, this could be an impetus to further evaluate plants from these families for anti-inflammatory activity.

CONCLUSION

This work has recognized that the methanolic extract of *D. metel*, *C. papaya, M. lucida* and *T. gleucescens.* employed traditionally to manage ailments and pain initiate by inflammation with significant anti-inflammation activity. The significant inhibition of iNOS in addition to the potent inhibition of NF-κB activity displayed by the methanol extract of *D. metel* indicates that this plant holds some anti-inflammatory constituents that necessitate further study. This work gives credence and validate the employment of some of these medicinal plants against inflammation. This affords some support i.e. scientific evidences to the traditional uses of these medicinal plants against inflammation.

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