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Contribution to the Valorization of Plants Used in the Management of Rheumatic Diseases in Burkina Faso

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Abstract

Joint pain is a real public health problem. According to recent studies, it is increasingly common in sub-Saharan Africa and represents a cause of greater loss of working days than accidents, heart disease and infections. The aim of this study was to study the pharmacochemical and therapeutic evidence of ten (10) plants used in the management of joint pain by traditional health practitioners in Ouagadougou. We conducted a meta-analysis of the data from December 2018 to September 2019. The anti-inflammatory activity of the ten (10) plants retained the maximum consensus internationally. *Trichilia emetica* Vahl (35.25%), *Guiera senegalensis* J.F.G.mel. (31%), *Calotropis procera* (Ait) Ait.F. (28.29%) and *Crescientia cujete* L. (25.12%) had more than 25% internationally reliability for their effects on joint pain. The structural analogy between conventional drugs and the molecules found in these plants has been confirmed. Additional studies should be carried out in order to improve and secure the use of these plants, which represent a prominent option in the therapeutic offer.

Keywords

Medicinal Plants, Anti-Inflammatory, Rheumatic Pathologies, Burkina Faso

1. Introduction

Rheumatism is a public health problem in developed countries. Sub-Saharan African countries are not concerned with because of priority diseases such as malaria, cardiovascular diseases and human immunodeficiency virus (HIV) infection. Over the last ten years, many studies have reversed this perception in low-income countries weakly affected by rheumatic diseases like rheumatoid arthritis (RA) [1]. For example, rheumatoid arthritis, which is chronic inflammatory and autoimmune rheumatism, had a world prevalence of 0.4% - 1% in 2015. In Burkina Faso, in-hospital frequency of 2.18% was reported by a study covering the period from 2006 to 2011 [2].

Rheumatism is a common chronic inflammatory disease, characterized by dysregulated inflammatory process in joint synovium that leads to the destruction of both cartilaginous and bones, resulting in pain, disability and destruction of articular structures. Complex autoimmune and inflammatory processes induce synovitis, swelling, and joint damage, after activation of components in both innate and adaptive immune systems. Rheumatism causes pain, weariness, and disability associated with a significant reduction in health-related, well-being and quality of life [3].

In community and economic fields, rheumatic diseases cause an invaluable loss of working time, greater than accidents, cardiovascular diseases and infections. The problem of Rheumatic-related disability is even pronounced in manual workers where entire musculoskeletal system is most solicited [4]. Repetition of painful crises and rheumatic disability compel patients to resort to both conventional, alternative or traditional medicine therapeutic care.

Therefore, more than 80% of the West African population resort to traditional medicine for treatment [5]. This therapeutic care is highly dependent on medicinal plants use and associated local knowledge [6] [7]. Cultural beliefs have a deep impact on choice of traditional medicine care by populations compared to economic reasons. Supply of health care and access to medicines is very weak or even non-existent and so expensive for African population. Moreover, despite the availability of generic drugs, many innovative treatments such as targeted therapy with monoclonal antibodies, remain inaccessible to low-income populations. Prices of conventional medicines range from two (2) dollars (anti-inflammatory drugs) to 100 dollars (targeted therapy) compared to traditional rarely exceed 1 dollar. Then, traditional medicine becomes a good alternative for health care coverage, especially in case of chronic pathology [5]. Hence, promoting traditional medicines and practices is encouraged by WHO and is included in public health policies in low-income countries. In Burkina Faso, out of 2067 species are listed and half have been registered with traditional uses including rheumatic diseases [2]. In a previous ethnobotanical survey, we reported that 73 species from 70 genera and 41 families are used by traditional health practitioners for rheumatism treatment in Ouagadougou, the political capital of Burkina Faso. The ten (10) most cited plants were selected for this study purpose which aims to provide factual evidences attesting their benefit in the treatment of rheumatism [2].

We then carried out a meta-analysis of the available scientific data pharmacologic properties of these plants in inflammatory joint pain relief. We also analyzed structural analogies between modern therapies compounds and plant metabolites to suggest qualitative structure-activity relation in pharmacological potential of these ten plants.

2. Material and Methods

2.1. Determination of Consensus Factors (FIC) and Fidelity Levels (FL) of Studied Plants

Determination of the informant consensus factor (FIC) and the fidelity level for identified plants was carried out online on 18 December 2018 according to method described by Hassan *et al.* [8]. We conducted a meta-analysis on the pharmacological properties of the 10 selected plants from December 2018 to September 2019.

Table 1 shows the different plant parts used in the treatment of rheumatic diseases, according to Youl *et al.* [2]. Research on scientific papers (26,595 articles) on plants has identified information on their chemical composition and pharmacological effects on rheumatic diseases (including joint pain).

2.1.1. Factor of Informant Consensus

The Informant Consensus Factor (FIC) represents independent variables that contribute to the agreement and consent in international scientific opinion. It was determined as previously described by Hassan *et al.* [8].

$$\mathrm{FIC} = \left(N_{ur} - N_t\right) / \left(N_{ur} - 1\right) \tag{1}$$

with: N_{ur}, scientific articles related to the therapeutic use of the plant;

N_t, plant species and for calculations, $N_t = 10$.

Table 1. Ten most used plants and parts for the management of rheumatic diseases.

Scientific name	Family	Plant drugs
Saba senegalensis (A. Dc) Pichon	Apocynaceae	Leaves
Parkia biglobosa (Jacq.)	Fabaceae-Mimosoideae	Bark
Guiera senegalensis J.F.G.mel.	Combretaceae	Leaves, roots
Calotropis procera (Ait) Ait.F.	Asclepiadaceae	Leaves, bark
Anogeissus leiocarpus (DC)	Combretaceae	Bark, roots
Khaya senegalensis (Desr) A. Juss	Meliaceae	Bark
Crescentia cujete L.	Bignoniaceae	Fruit
Annona senegalensis Pers.	Annonaceae	Leaves, roots
Trichilia emetica Vahl	Meliaceae	Roots
Zizyphus mauritiana Lam.	Rhamnaceae	Bark, roots

Data were analyzed on Microsoft Excel 2013 and FIC values range from 0 to 1, where 1 indicates the highest level of consensus. The thresholds for this data analysis have been set at 5% ($\alpha = 0.05$) which represent the probability of similar use in therapeutics claimed worldwide.

2.1.2. Fidelity Level

Fidelity Level (FL) represents the accuracy of the claimed medicinal use [9].

$$\mathrm{FL} = \left[\left(X_1 + X_2 + X_3\right)/Y\right] \times 100. \tag{2}$$

with: X_1, scientific articles combining plant and joint pain; X_2, scientific articles combining plant and anti-inflammatory; X_3, scientific articles combining plant and antirheumatic; Y, number of all citations for the name of the plant only.

Data was analyzed on Microsoft Excel 2013, and thresholds for data analysis have been set at 25% which represent the strength of fidelity showing that this indication is well recognized for this plant.

2.2. Study of Structural Analogies between Selected Plant Secondary Metabolites and Antirheumatics

Drugs used as antirheumatics for structural analogies study, include nonsteroidal anti-inflammatory drugs (salicylates, fecates, arylpropionic, arylacetic, oxicams, coxibs), anti-inflammatory steroids (Glucocorticoids), analgesics (morphine, paracetamol, metamizole), and antifouling agents (colchicine). First, basic chemical skeletons of these antirheumatic drugs were identified based on those of the three (03) major categories of secondary metabolites (phenolic compounds, nitrogen compounds and terpenic compounds). Secondly, documented chemical composition of plants allowed comparison with modern drugs basic chemical skeletons in order to identify potential structural analogies. The state of knowledge on these plants (pharmacological activity and chemical constituents) was carried out on scientific search engines such as PUBMED, Medline, EMBASE, Science Direct and Google scholar databases using keywords (plant names, joint pain, anti-inflammatory properties)

3. Results and Discussion

3.1. Determination of the Informant Consensus Factors and Fidelity Levels of Identified Plants

Review on scientific articles related to pharmacological activities of selected plants is presented in **Table 2**.

Zizyphus mauritiana Lam. was subject to the largest number of scientific publications (5610) while *Trichilia emetica* Vahl had 644 publications. Anti-inflammatory use of these ten (10) plants retain an informant consensus factor up to 1. This suggests a scientific agreement and consent for anti-inflammatory properties of these plants. The ethno-medical and ethno-pharmacological evidence of these plants used for their anti-inflammatory properties could thus be confirmed by scientific publications analysis.

Table 2. Informant consensus factors and fidelity levels on anti-inflammatory and antirheumatic properties of the ten (10) plants used by Health Tradipraticians in Ouagadougou.

Scientific name	Number of citations for plant only	Number of citations for plant and joint pain	Frequency of use in joint pain (%)	Number of plant and anti-inflammatory citations	Frequency of use as anti-inflammatory (%)	Plant and antirheumatic	Frequency of use as antirheumatic (%)	Fidelity Level (%)
Saba senegalensis (A. Dc) Pichon	1320	61	4.62	110	8.33	6	0.45	13.41
Parkia biglobosa (Jacq.)	2660	83	3.12	352	13.23	10	0.38	16.73
Guiera senegalensis **J.F.G.mel.**	871	36	4.13	232	26.64	2	0.23	**31**
Calotropis procera **(Ait) Ait.F.**	5150	402	7.81	1030	20	25	0.49	**28.29**
Anogeissus leiocarpus (DC)	3380	87	2.57	481	14.23	8	0.24	17.04
Khaya senegalensis (Desr) A. Juss	3710	148	3.99	433	11.67	9	0.24	15.90
Crescentia cujete **L.**	860	82	9.53	132	15.35	2	0.23	**25.12**
Annona senegalensis Pers.	2390	117	4.90	299	12.51	8	0.33	17.74
Trichilia emetica **Vahl**	644	48	7.45	176	27.33	3	0.47	**35.25**
Zizyphus mauritiana Lam.	5610	307	5.47	687	12.25	8	0.14	17.86
Factor of Informant Consensus								
N_{ur}	-	1371	-	3932	-	81	-	-
FIC	-	0.99	-	**1.00**	-	0.89	-	-

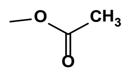
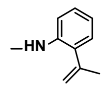
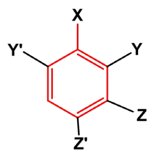
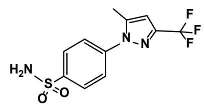
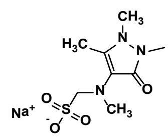
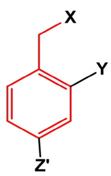
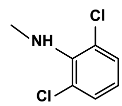
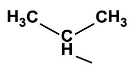
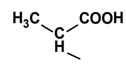
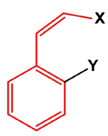
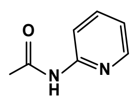
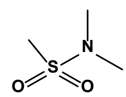
N_{ur} = articles related to the therapeutic use of plant, FIC = factors of informant consensus.

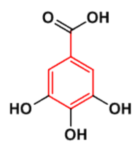
Estimation of fidelity level of use on inflammatory joint pain management showed 4 plants with more than 25% fidelity of claimed on inflammatory joint pain such as *Trichilia emetica* Vahl (35.25%), *Guiera senegalensis* J.F.G.mel. (31%), *Calotropis procera* (Ait) Ait.F. (28.29%) and *Crescientia cujete* L. (25.12%). Indeed, *Trichilia emetica* Vahl root powder mixed with potassium hydroxide and water traditionally cures inflammation [5]. *Guiera senegalensis* leaves extracts showed an analgesic effect and are widely used against rheumatism [7]. *Calotropis* species are used for the treatment of pain and rheumatism, like roots used against rheumatism, and latex and leaves used in the treatment of joint pain. So, several studies provide evidence of Calotropis species analgesic, anti-inflammatory and anti-nociceptive properties [10]. *Crescientia cujete* L. extracts exhibit anti-inflammatory activities [11] [12].

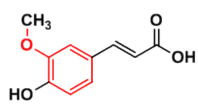
3.2. Study of Structural Analogies between Selected Plants Secondary Metabolites and Antirheumatics

Structural analogies between secondary metabolites found in selected plants and antirheumatic drugs are presented in **Table 3** and **Table 4**. Illustration of chemical compounds found in medicinal plants showing similar basic chemical skeletons as anti-rheumatic drugs are provided in **Figure 1**.

Table 3. Basic skeleton of phenolic derivatives found in antirheumatic drugs.

Antirheumatic drugs	Therapeutic class	Basic skeleton	Substituents X	Substituents Y	Substituents Z	Substituents Y'	Substituents Z'
Acetylsalicylic acid			-COOH		-	-	-
Mefenamic acid	Nonsteroidal anti-inflammatory drugs			$-CH_3$	$-CH_3$	-	-
Celecoxib			-		-	$-CH_3$	-
Paracetamol		C_6-C_1	-OH	-	-	-	—HN–COCH$_3$
Metamizole	Analgesic		-	-	-		-
Diclofenac			-COOH		-	-	-
Ibuprofen	Nonsteroidal anti-inflammatory drugs	C_6-C_2		-	-	-	
Oxicams		 C_6-C_3			-	-	-





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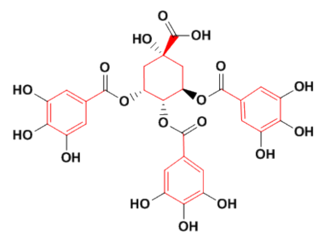
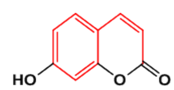
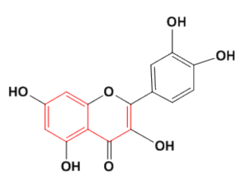
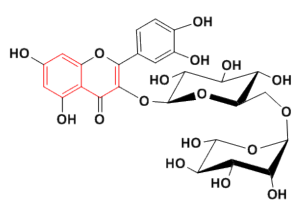


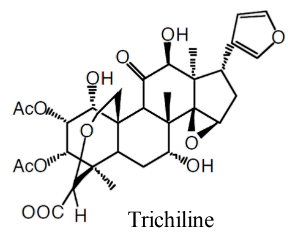
Acide 3,4,5-tri-O-galloylquinique
(3)



Coumarine
(4)



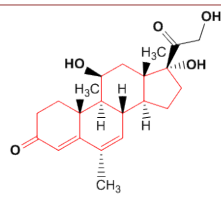
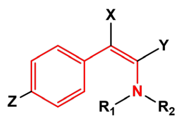
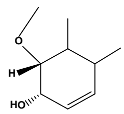
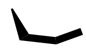
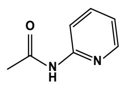
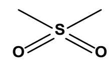
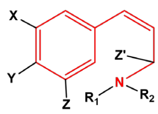
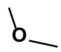
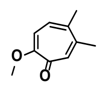
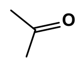




Trichiline
(7)

Figure 1. Examples of selected plant secondary metabolites showing a basic chemical skeleton similar to antirheumatic drugs.

Table 4. Basic skeleton corresponding to terpenic and nitrogen compounds found in antirheumatic drugs.

Antirheumatic drugs	Therapeutic class	Basic skeleton	Substituents						Chemical groups of secondary metabolites
			X	Y	Z	Z’	R1	R2	
Glucocorticoid	Inflammatory Steroidal								Terpenoid
Morphine	Analgesic				-OH	-		$-CH_3$	
Oxicams	Nonsteroidal anti-inflammatory drugs	**C_6-C_2-N**	-OH		-	-		$-CH_3$	Nitrogenous derivatives
Colchicine	Antigout	 **C_6-C_3-N**					H		

3.2.1. Basic Chemical Skeletons Corresponding to Phenolic Compounds

Analgesics and anti-inflammatories drugs used in the treatment of rheumatic pathologies presented a basic chemical skeleton like C_6-C_1, C_6-C_2 and C_6-C_3 type (**Table 3**), close to those of plant phenolic compounds [13]. Study of chemical compounds found in plants with the highest level of agreement for inflammatory joint pain care also indicates the presence of compounds showing similar basic skeletons C_6-C_1 and C_6-C_3 type.

1) C_6-C_1 Basic Chemical Skeleton Molecules

Trichilia emetica Vahl contains C_6-C_1 phenolic acids such as gallic acid (1) (**Figure 1**) in the root bark [14]. Gallic acid shows anti-inflammatory properties by decrease expression and release of pro-inflammatory and inflammatory mediators, such as bradykinine, substance P, Cyclooxygenase 2 (COX-2), Nuclear Factor-kappa B (NF-κB), Interleukin-2 (IL-2), Interleukin-4 (IL-4), Interleukin-5 (IL-5), Interferon gamma (IFN-γ) and Tumor Necrosis Factor α (TNF-α). It also inhibits polymorphonuclear agents involved in the inflammatory response and decreases the activity of myeloperoxidase (MPO) [15] [16]. Root also contains ferulic acid (2) (**Figure 1**) [17]. Ferulic acid showed promising anti-inflammatory activity (inhibition of TNF-α, Interleukin-6 (IL-6) and COX-2). Gallic acid, ferulic acid demonstrated inhibition of xanthine oxidase [14]. *Guiera senegalensis* J.F.G.mel contains nine galloylquinic acids, namely 3-O-, 5-O-, 1,3-di-O-, 3,4-di-O-,3,5-di-O-,4,5-di-O-,1,3,4-tri-O-,3,4,5-tri-O- and 1,3,4,5-tetra-O-galloylquinic isolated by column chromatography and HPLC from different plant parts. Among these nine (09) galloylquinic acids, 3,4,5-tri-O-galloylquinic is a new ethyl ester of polyphenol acid (3) (**Figure 1**). Gallic acid has also been isolated from leaves [18]. In addition, 3,4,5-tri-O-galloylquinic acid isolated from *Guiera senegalensis* J.F.G.mel. has showed to exhibit anti-HIV activity [19]. Phenols are present in leaves of *Calotropis procera* (Ait) Ait.F. and in *Crescientia cujete* L. fruits [10]. It is recognized that phenolic compounds proceed in the same way as NSAIDs, and some of them inhibit other pro-inflammatory mediators [13].

2) C_6-C_3 Basic Chemical Skeleton Molecules

Guiera senegalensis J.F.G.mel. leaves extracts contain coumarin (4) and flavonoids such as quercetin (5) and rutin (6) (**Figure 1**) [19]. *Trichilia emetica* Vahl root barks also contain flavonoids such as rutin (6) [20]. *Calotropis procera* (Ait) Ait.F. leaves and barks contain flavonoids, mainly rutin (6) [20] which exhibit anti-inflammatory properties by reduction of the production of pro-inflammatory cytokines and inhibition of xanthine oxidase. *In vivo*, quercetin (5) has been shown to have anti-inflammatory properties by attenuating lipid peroxidation, platelet aggregation and capillary permeability. It also inhibits cyclooxygenases (COX), lipoxygenase (LOX) and lipopolysaccharide (LPS) which induces the production of TNF-α in macrophages and the production of IL-8 [21]. *Crescientia cujete* L. contains flavonoids in these fruits [22] which have anti-inflammatory properties [21].

3.2.2. Basic Chemical Skeletons Corresponding to Terpenic Compounds

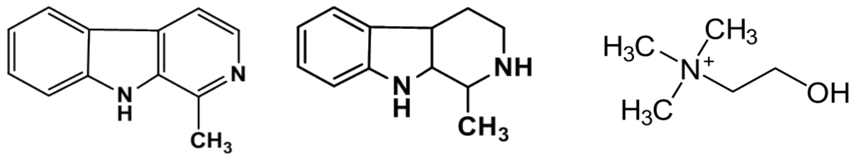
Drugs used in inflammatory joint pain care present basic chemical skeletons close to steroid-like triterpene derivatives as corticosteroids and their derivatives (**Table 4**). Scientific publications indicate that many plant-derived triterpenes have anti-inflammatory properties [23].

Study of chemical compounds found in plants with the highest level of agreement for inflammatory joint pain care also indicates the presence of compounds showing similar basic skeletons of terpenoids. Steroid-like triterpene compounds have been identified in *Trichilia emetica* Vahl [24], *Guiera senegalensis* J.F.G.mel. [25], *Calotropis procera* (Ait) Ait.F. [26]. Similarly, limonoid type, a modified triterpenic compounds such as tetranortriterpenoids trichiline (7) (**Figure 1**) were found in the root bark of *Trichilia emetica* Vahl [24] and saponoside type were found in *Crescientia cujete* L. fruits [22]. Limonoids showed a strong anti-inflammatory activity [23].

3.2.3. Basic Chemical Skeletons Corresponding to Nitrogen Compounds

Observations of chemical structures indicated that morphine and piroxicam have basic chemical skeletons of C_6-C_2-N type while colchicine would be of C_6-C_3-N type (**Table 3**) close to phenylalanine-derived compounds. Many alkaloids, especially the iso-quinoline alkaloids, exhibiting the same basic skeletons, are known to have anti-inflammatory and analgesic properties [27].

Study of chemical compounds found in plants with the highest level of agreement for inflammatory joint pain care also indicates the presence of nitrogen



Harmane (8) | Tetrahydroharmane (9) | Choline (10)

Figure 2. Examples of nitrogenous derivatives presenting anti-inflammatories properties found in selected plants used by tradipraticians and whose basic chemical skeleton differed from that of anti-rheumatic drugs.

compounds in three (03) plants in exception of *Trichilia emetica* Vahl. Basic chemical skeletons of C_6-C_2-N and C_6-C_3-N type, similar to nitrogen compounds have not been identified in *Guiera senegalensis* J.F.G.mel. [18], *Calotropis procera* (Ait) Ait.F. [10], and *Crescientia cujete* L. [11]. Nevertheless, we noted in *Guiera senegalensis* J. F. G. mel the presence of indolic alkaloids β-carboline type as harmalane, harmane and tetrahydroharmane (**Figure 2**) [28]. These compounds demonstrated anti-inflammatory activities by suppressing nitric oxide production and secretion of pro-inflammatory cytokines [29]. Similarly, nitrogen compounds like choline has been identified in the latex of the leaves of *Calotropis procera* (Ait) Ait.F. Choline is a quaternary ammonium-like proto-alkaloid [30] that showed anti-inflammatory effects. We could not identify structural analogies between these nitrogen molecules, which potent anti-inflammatory properties have been already demonstrated and modern antirheumatics.

4. Conclusions

Determination of informing consensus factor and the fidelity level attest to the efficiency of selected plants for traditional care of joining pain and give evidence for a scientifically recognized worldwide. Study of structural analogies between plants compounds used in the treatment of inflammatory rheumatic diseases and modern drugs' basic chemical skeleton indicates many similarities. Phenolic compounds C_6-C_1, C_6-C_3 type, similar to basic skeletons of anti-inflammatory and analgesic are found in selected plants. Then, steroid-like terpenic compounds with basic chemical skeleton close to corticosteroids have been identified in *Trichilia emetica* Vahl, *Guiera senegalensis* J.F.G.mel., *Calotropis procera* (Ait) Ait.F. These observations strengthen scientific basis for the use of *Trichilia emetica* Vahl, *Guiera senegalensis* J.F.G.mel., *Calotropis procera* (Ait) Ait.F. and *Crescientia cujete* L. in inflammatory joint pain treatment.

The subsequent evaluation of therapeutic equivalences will allow the development of plant-based phytomedicines, standardized in therapeutic equivalent of modern treatments per gram of dry plant material. Evaluation of QSAR of plant compounds as indolic alkaloids and modified triterpenic compounds with potent anti-inflammatory properties could give models for drug design and discovery in the area of new therapies development.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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