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

Aminata P. Nacoulma¹, Gontili Reine Elodie Karambiri¹, Naamwin-So-Bawfu Romaric Meda¹, Mìndiédiba Jean Bangou², Moussa Ouedraogo¹, Dieu-Donné Ouedraogo⁴

¹Département des Sciences Pharmaceutiques Appliquées, UFR Sciences de la Santé, Université Joseph Ki-Zerbo, Ouagadougou, Burkina Faso
²Training and Research Unit in Sciences and Technology (UFR-ST), Department of Biochemistry and Microbiology, University of Nazi BONI, Bobo-Dioulasso, Burkina Faso
³Laboratory for Research and Education in Animal Health and Biotechnology (LARESBA), University of Nazi BONI, Bobo-Dioulasso, Burkina Faso
⁴Département de Médecine et Spécialités Médicales, UFR Sciences de la Santé, Université Joseph Ki-Zerbo, Ouagadougou, Burkina Faso

Email: natanac5@gmail.com

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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 pharmaecochemical 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 Crescentia 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].

\[
FIC = \left( \frac{N_{wr} - N_r}{N_{wr} - 1} \right)
\]

with: \(N_{wr}\) scientific articles related to the therapeutic use of the plant; \(N_r\) plant species and for calculations, \(N_r = 10\).

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].

$$\text{FL} = \left[ \frac{X_1 + X_2 + X_3}{Y} \right] \times 100.$$  \hspace{1cm} (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 anti-rheumatic; $Y$, 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-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

|                | $N_w$ | FIC     |
|----------------|-------|---------|
| $N_w$          | 1371  | 0.99    |
| FIC            | 1.00  | 0.89    |

$N_w$ = 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 *Crescentia 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]. *Crescentia 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 |
|---------------------|-------------------|----------------|--------------|
| Acetylsalicylic acid | Nonsteroidal anti-inflammatory drugs | -COOH | X |-CH3 | Y |-CH3 | Z |-CH3 | Y' |-CH3 | Z' |-CH3 |
| Mefenamic acid      | Nonsteroidal anti-inflammatory drugs | -CH3 | X |-CH3 | Y |-CH3 | Z |-CH3 | Y' |-CH3 | Z' |-CH3 |
| Celecoxib           |                   | C6-C1- | X |-CH3 | Y |-CH3 | Z |-CH3 | Y' |-CH3 | Z' |-CH3 |
| Paracetamol         | Analgesic         | -OH | X |-CH3 | Y |-CH3 | Z |-CH3 | Y' |-CH3 | Z' |-CH3 |
| Metamizole          |                   | - | X |-CH3 | Y |-CH3 | Z |-CH3 | Y' |-CH3 | Z' |-CH3 |
| Diclofenac          | Nonsteroidal anti-inflammatory drugs | -COOH | X |-CH3 | Y |-CH3 | Z |-CH3 | Y' |-CH3 | Z' |-CH3 |
| Ibuprofen           | Nonsteroidal anti-inflammatory drugs | -CH3 | X |-CH3 | Y |-CH3 | Z |-CH3 | Y' |-CH3 | Z' |-CH3 |
| Oxicams             |                   | C6-C3- | X |-CH3 | Y |-CH3 | Z |-CH3 | Y' |-CH3 | Z' |-CH3 |

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 |
|---------------------|-------------------|----------------|--------------|------------------------------------------|
| Glucocorticoid      | Inflammatory      |                | X            | Terpenoid                                |
|                     | Steroidal         |                | Y            |                                          |
| Morphine            | Analgesic         |                | Z            |                                          |
|                     | Nonsteroidal      |                | Z'           |                                          |
| Oxicams             | Nonsteroidal      |                | R1           |                                          |
|                     | anti-inflammatory |                | R2           |                                          |
| Colchicine          | Antigout          |                | 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 C₆-C₁, C₆-C₂ and C₆-C₃ 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 C₆-C₁ and C₆-C₃ type.

1) C₆-C₁ Basic Chemical Skeleton Molecules

*Trichilia emetica* Vahl contains C₆-C₁ 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-,1,3,4,5-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 *Crescienia 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) C₆-C₃ 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]. *Crescienia 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 tetrnortriterpenoids trichiline (7) (Figure 1) were found in the root bark of *Trichilia emetica* Vahl [24] and saponoside type were found in *Crescienia 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 C₆-C₂-N type while colchicine would be of C₆-C₃-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.
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Figure 2. Examples of nitrogenous derivatives presenting anti-inflammatory 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 C₆-C₂-N and C₆-C₃-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, harmaine and tetrahydroharmaine (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 C₆-C₁, C₆-C₃ 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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