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Hunt For Bioactive Phytomolecules Against Rheumatoid Arthritis Based On Investigation And Documentation Of Traditional Polyherbal Formulations Used By Indigenous Communities In Chhattisgarh, India

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Abstract
Rheumatoid arthritis (RA) - an autoimmune disorder (AD), primarily affects the joints leading to their deformities and destruction. In addition, RA leads to the increased risk for cardiovascular disease, lymphoma, and also death in extreme cases. Excluding few sporadic studies, there is complete paucity of information on prevalence of RA in India and absolutely nothing is known for the Chhattisgarh State that achieved the status of a new geopolitical entity in 2000. In the present study, we designed a protocol for documenting traditional knowledge (TK) currently in use by the indigenous tribal communities for curing RA in those districts. The local names of the medicinal plants were recorded. Medicinal plants, plant parts used and polyherbal formulations were also collected and studied for preservation and analysis purposes. The analysis of data revealed that eighty-one polyherbal formulations were used for the curing RA that included 115 plant species belonging to 57 families. The work is currently under progress to pinpoint the exact phytochemical(s) for control and cure of RA. Till date no potential allopathic drug is available for complete cure of RA. Therefore, the present work is promising and might help in the discovery of potential therapeutic molecule(s) for the control and cure of RA.

Keywords: Rheumatoid arthritis (RA), Traditional healer, Traditional healing practices, Polyherbal formulation, Medicinal plants.

Introduction

The rheumatoid arthritis (RA) - an autoimmune disorder (AD), primarily affects the joints leading to their deformities and destruction [1]. It affects people of all ages, although the exact cause is unknown. It is frequent in women comparable with men in a ratio 3:1 [2]. A study, conducted about two and a half decades ago in the rural areas adjacent to Delhi, revealed 0.75 percent prevalence of RA in Indian population [3]. A recent study based on the data collected from 55000 subjects at 12 different sites reported it to be 0.34 percent [4]. Excluding these two sporadic studies, there is complete paucity of information on prevalence of RA in India and absolutely nothing is known for the Chhattisgarh State that achieved the status of a new geopolitical entity in 2000.

Rheumatoid arthritis leads to the increased risk for cardiovascular disease, lymphoma, and also death in extreme cases [5]. It is typically associated with high levels of oxidative stress and inflammatory responses. Current treatment of RA is carried out using wide variety of medicines, such as steroidal and/or non-steroidal anti-inflammatory (NSAID) drugs. These are potent biological agents that target specific immune and inflammatory pathways through inhibiting □-TNF and interleukin-1 receptors [6]. Acetaminophen is the most frequently used NSAID with a high dose of 4000 mg/day. Etanercept, infliximab and rituximab represent a few examples of TNF-alpha inhibitors used for the treatment in case of

severity [7,8]. Anakinra (an interlukin-1 receptor antagonist) [9] and methotrexate are other therapeutic choices for RA [10]. Tramadol and opioids, such as morphine is highly recommended in extreme conditions [11].
The aforesaid drugs are routinely used in the majority of RA cases, including the severe ones. Unfortunately, the use of these drugs in arthropathies is associated with numerous and frequently serious side effects [12], such as ulcerations in gastrointestinal tract, hemorrhagic events, and NSAID induced nephrotoxicity [13]. The TNF-alpha inhibitors trigger hypersensitivity reactions and auto-immune responses (e.g., lupus-like syndrome) [14]. There is also an increased risk of severe infection that affects the respiratory tract and induces fatal cytopenia. These pathological conditions are attributed to use of drugs, such as anakinra, rituximab, abatacept [15,16] and methotrexate [17]. Therefore, the clinicians are looking for alternative therapeutics with the least adverse effects.
Of late, there is renewed interest in phytomedicines as they lack severe adverse effects with moderate to high efficacy [18]. These phytoremedials may have beneficial effects with reference to both diagnosis and prognosis [19]. In past few years, there has been an increased awareness for the use of traditional medicines in curing of various diseases globally [20, 21]. A majority of the world population follows traditional medicine, including about 65% of the Indian rural population that follows traditional medicinal practices to meet their primary health care needs [21]. The use of phytomedicine and its validation is gaining momentum for its revival. The scientists of developing countries are also paying attention for the development of drugs based on the traditional medicinal knowledge accumulated from the practice seeping from generation to generation. Although practice of traditional medicinal system is widespread among the tribes of Chhattisgarh, there is lack of systematic documentation of the intangible oral traditions of health care system. The exact number of traditional healers is not known. We also know nothing about the formulations and their dosage regimen used for curing various diseases, including RA [22, 23].
Therefore, we designed a study involving the documentation of traditional knowledge (TK) currently in use by the indigenous tribal communities of Chhattisgarh for curing RA in those districts.

Materials and Methods

Selection
The Chhattisgarh is situated in central India with Raipur as its capital. It gained statehood after it was carved out from Madhya Pradesh with a geographical area of 135,195 sq km. Chhattisgarh is a landlocked state sharing its borders with seven other states. About 44% of the State's area is under forest cover [22, 23]. The herbal State of Chhattisgarh has the densest forests in India with rich wildlife and medicinal herbs.

Identification of medicinal plants and formulations
Name of the medicinal plants, plant part used, mode of preparation & other associated material (if any) used for preparation of formulations, folklore and taboo and cultural significance associated with it, dosage form and so forth were also documented in detail.

Statistical analyses of Data
The data was further subjected to statistical validation.

Results
From the in-depth literature analysis, we discovered that a large number of medicinal plants comprising of 115 plant species belonging to 57 families (Table 1) are used for curing RA in the form of 81 polyherbal formulations. The family Fabaceae represented the maximum number of plant species, followed by Apocynaceae, Euphorbiaceae, Lamiaceae, Malvaceae, Solanaceae, Zingiberaceae and so on (Figure 1). Majority of medicinal plants belonged to herbs (37.39%), followed by tree (30.43%), shrub (18.26%) and climber (13.91%).

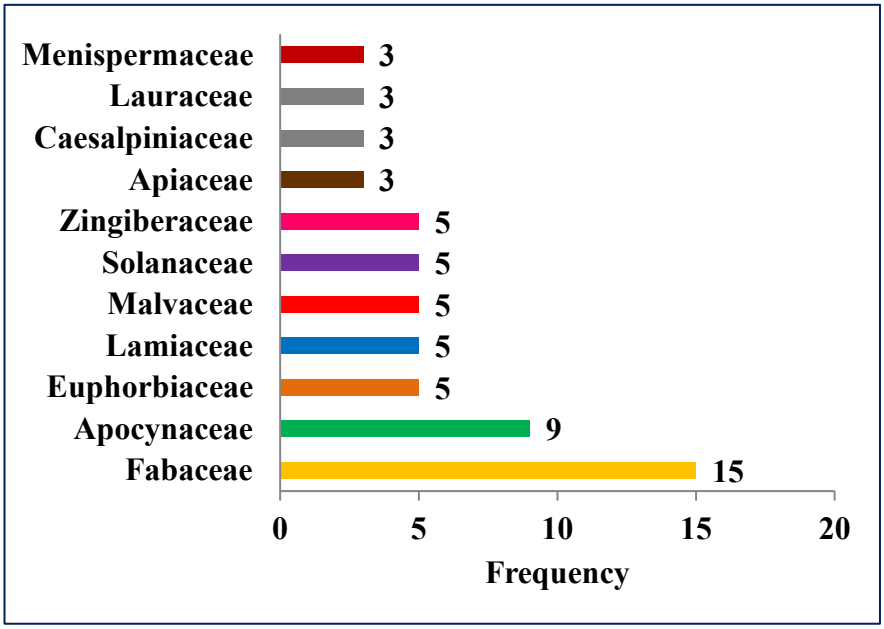

Fig 1. Families of medicinal plants reported for curing RA in surveyed districts

All the medicinal plant species were collected from the surrounding as well as from distant forest areas, used by the traditional healers for curing RA. The dose prescribed by the traditional healers depends upon age, physical status and health conditions of the patient. The present study revealed that roots are the most used plant part for curing RA in various reported formulations by traditional healers. Other frequently used plant parts were leaf, bark, fruit, seed and tuber(Figure2).

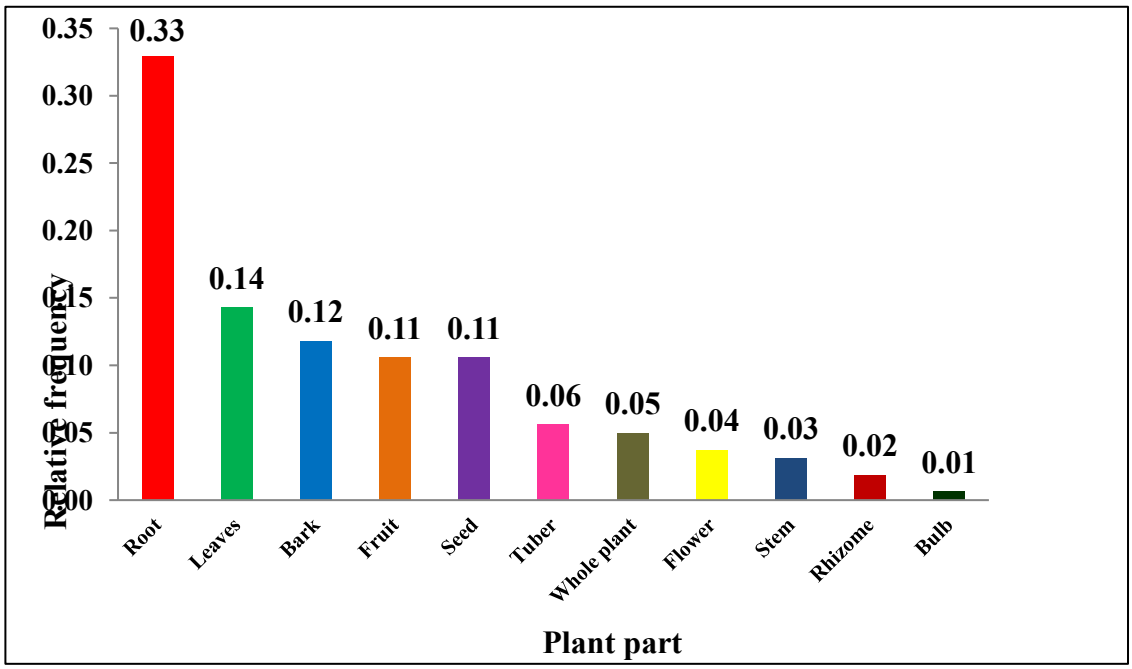

Fig 2. Plant parts used for curing RA in surveyed districts of Chhattisgarh

Table 1. List of medicinal plants used for curing RA in surveyed districts of Chhattisgarh

S. No.	Local name	Botanical name	Family	Habit	Plant part used
1	Van Kapaas	*Abelmoschus moschatus* Medik.	Malvaceae	Herb	Seed, root
2	Gunj	*Abrus precatorious* L.	Fabaceae	Climber	Root, Stem, Seed
3	Kadam kapoor	*Acacia farnesiana* (L.) Willd.	Mimosaceae	Tree	Bark
4	Apamarg	*Achyranthes aspera* L.	Amaranthaceae	Herb	Leaf
5	Bach	*Acorus calamus* L.	Acoraceae	Herb	Root
6	Bel	*Aeglemarmelos* (L.) Correa	Rutaceae	Tree	Root, fruit, leaves
7	Lahsun	*Allium sativum* L.	Liliaceae	Herb	Bulb
8	Banrakas	*Alocasiaindica* (Roxb.) Schott.	Araceae	Herb	Root, leaves, tuber
9	Chhatim	*Alstonia scholaris (*L.) R.Br.	Apocynaceae	Tree	Leaves, bark
10	GundruSaag	*Alternanthera sessilis* (L.) R. Br. *ex* DC.	Amaranthaceae	Herb	Root
11	ChipiJadi	*Alysicarpus monilifer* (L.) DC.	Fabaceae	Herb	Root
12	Bhuineem	*Andrographis paniculata* (Burm. *f* .)Wallich*ex* Nees	Acanthaceae	Herb	Whole plant, Root, Leaf
13	Mungfali	*Arachis hypogea* L.	Fabaceae	Herb	Seed
14	Satavari	*Asparagus racemosus* Willd.	Asparagaceae	Climber	Tuber
15	Dantimool	*Baliospermum montanum* (Willd.) Muell. Arg.	Euphorbiaceae	Shrub	Root
16	Mohlayan	*Bauhinia vahlii* Wt&Arn.	Caesalpiniaceae	Climber	Leaves
17	Koynaar	*Bauhinia variegate* L.	Caesalpiniaceae	Tree	Root
18	Punarnava	*Boerhavia diffusa* L.	Nyctaginaceae	Herb	Root
19	Gataran	*Caesalpinia bonduc* (L.) Roxb.	Caesalpiniaceae	Shrub	Seed
20	SafedPhurhar	*Calotropis gigantea* (L.) R.Br.	Apocynaceae	Shrub	Root, Leaf, Seed
21	Phurhar	*Calotropis procera* (Aiton) R. Br.	Apocynaceae	Shrub	Root
22	Ganja	*Cannabis sativa* L.	Cannabaceae	Herb	Fruit
23	Mirch	*Capsicum annum* L.	Solanaceae	Herb	Fruit
24	Kumbhi	*Careya arborea* Roxb.	Lecythidaceae	Tree	Leaves
25	Karonda	*Carissa carandas* L.	Apocynaceae	Shrub	Root
26	Chilhi	*Casearia tomentosa* Roxb.	Flacourtiaceae	Tree	Root
27	Kujuri	*Celastrus paniculatus* Willd.	Celastraceae	Climber	Root
28	SafedMusli	*Chlorophytum tuberosum* (Roxb.)Baker	Asparagaceae	Herb	Root
29	Kala DeshiChana	*Cicera rietinum* L.	Fabaceae	Herb	Fruit
30	Tejpatta	*Cinnamomum tamala* Nees & Eberm	Lauraceae	Tree	Leaves
31	Dalchini	*Cinnamomum zeylanicum* Blume	Lauraceae	Tree	Bark
32	Naarkoriya	*Cissampelos pareira* L.	Menispermaceae	Climber	Root
33	Bharangi	*Clerodendron serratum* (L.) Moon	Verbenaceae	Herb	Root
34	Keokanda	*Costus speciosus* (J.Koenig) Sm.	Costaceae	Herb	Rhizome
35	Sun beej	*Crotalaria juncea* L.	Fabaceae	Shrub	Seed
36	Watnashan	*Croton roxburghii* Balak.	Euphorbiaceae	Tree	Root, bark
37	Kali musli	*Curculigoorchioides*Gaertn.	Hypoxidaceae	Herb	Root, tuber
38	Aamihaldi	*Curcuma amada* Roxb.	Zingiberaceae	Herb	Root, flower
39	Kali haldi	*Curcuma caesia* Roxb.	Zingiberaceae	Herb	Root
40	Haldi	*Curcuma longa* L.	Zingiberaceae	Herb	Rhizome
41	Parhi	*Cyclea barbata* Miers	Menispermaceae	Climber	Tuber
42	Lemon grass	*Cymbopogon citrates* (DC.) Stapf	Graminaceae	Herb	Whole plant

43	Dhatura	*Datura metel* L.	Solanaceae	Shrub	Root, fruit, seed, leaves
44	Shivlingi	*Diplocyclos palmatus* (L.) Jeffrey	Cucurbitaceae	Climber	Fruit
45	Medhimool	*Dregea volubilis* (L. f.) Benth. *ex* Hook. *f.*	Apocynaceae	Climber	Bark, root
46	Elaichi	*Elettaria cardamomum* (L.) Maton	Zingiberaceae	Herb	Seed
47	Bayvidang	*Embelia ribes* Burm. *f.*	Myrsinaceae	Climber	Fruit
48	Amla	*Emblica officinalis* Gaertn.	Phyllanthaceae	Tree	Fruit
49	Durlabha	*Fagonia Arabica* L.	Zygophyllaceae	Herb	Bark, leaves
50	Bargad	*Ficus bengalensis* L.	Moraceae	Tree	Leaves
51	Pipal	*Ficus religiosa* L.	Moraceae	Tree	Bark
52	Balrajjadi	*Flemingia nana* Roxb.	Fabaceae	Shrub	Root
53	Sabarbhanj	*Flemingia strobilifera* (L.) R. Br.	Fabaceae	Shrub	Root, stem
54	Kharhar	*Gardenia turgid* Roxb.	Rubiaceae	Tree	Root
55	Kalihari	*Gloriosa superba* L.	Colchicaceae	Climber	Tuber
56	Gulshankhari	*Grewia hirsute* Vahl.	Malvaceae	Shrub	Root
57	Aithi	*Helicteres isora* L.	Malvaceae	Shrub	Fruit
58	Kamraj	*Helminthostachys zeylanica* L. Hook.	Ophioglossaceae	Herb	Root, seed
59	Koriya	*Holarrhena antidysentterica* Wallich.	Apocynaceae	Tree	Root, bark, flower
60	Mokhlakantaa	*Hygrophila auriculata* (K. Schum.) Heine.	Acanthaceae	Herb	Whole plant
61	Bhawarmali	*Hymenodictyon excelsum* Wall.	Rubiaceae	Tree	Root
62	Puskarmool	*Iris germanica* Linn.	Iridaceae	Herb	Tuber
63	Ratanjot	*Jatropha curcas*L.	Euphorbiaceae	Tree	Stem, bark
64	Maida	*Litsea glutinosa* (Lour.) C.B.Rob.	Lauraceae	Tree	Bark
65	Kala mahajal	*Lygodium flexuosum (*L.) Sw.	Schizaeaceae	Climber	Root
66	Kulthiya	*Macrotyloma uniflorum* (Lam) Verdc	Fabaceae	Herb	Root
67	Mahua	*Madhuca indica* Roxb.	Sapotaceae	Tree	Leaves, root, bark, flower
68	Aam	*Mangifera indica*Linn.	Anacardiaceae	Tree	Bark
69	Pudina	*Mentha spicata* L.	Lamiaceae	Herb	Leaves
70	Champa	*Michelia champaca* L.	Magnoliaceae	Treee	Leaves
71	Chaap	*Moghania chappar* (Benth.) Kuntze	Fabaceae	Shrub	Whole plant
72	Ban karela	*Momordica dioica* Roxb. Ex Willd.	Cucurbitaceae	Climber	Root, tuber, fruit
73	KawachKini	*Mucuna pruriens* (L.) DC.	Fabaceae	Climber	Fruit
74	Jayphal	*Myristica fragrans* Hautt.	Myristicaceae	Tree	Fruit, seed, leaves
75	Tobacco	*Nicotiana tabacum*L.	Solanaceae	Herb	Leaves
76	Bhuikosam	*Ochna obtusata* DC.	Ochnaceae	Tree	Root, fruit
77	Tulsi	*Ocimum sanctum* Linn.	Lamiaceae	Shrub	Leaves
78	Karnidhan	*Oryza sativa* L. ssp. Japonica	Poaceae	Herb	Seed
79	Tinpaniya	*Oxalis corniculata* Linn.	Oxalidaceae	Herb	Leaves
80	Afeem	*Papaver somniferum* L.	Papaveraceae	Herb	Bark, fruit
81	Bhojraj	*Peucedanum dhana* Ham.	Apiaceae	Herb	Root
82	Tejraj	*Peucedanum nagpurense* C. B. Clarke	Apiaceae	Herb	Root, whole plant
83	Urad	*Phaseolus mungo* Linn.	Fabaceae	Herb	Seed
84	Bhuiamla	*Phyllanthus niruri* L.	Euphorbiaceae	Herb	Whole plant

86	Kutki	*Picorhiza kurroa* Royle ex Benth.	Plantaginaceae	Herb	Leaf, Root
87	Kali mirch	*Piper nigrum* L.	Piperaceae	Climber	Fruit
88	Bantulsa	*Plectranthus incanus* Link	Lamiaceae	Herb	Leaves
89	Rasnajadi	*Plumeria acutifolia* L.	Apocynaceae	Shrub	Root
90	Karanj	*Pongamia pinnata* Linn.	Fabaceae	Tree	Seed
91	Raktchandan	*Pterocarpus santalinus* L.f.	Fabaceae	Tree	Bark
92	Patalkumhda	*Pueraria tuberosa* (Willd.) DC.	Fabaceae	Climber	Tuber
93	Sarpagandha	*Rauvolfia serpentine* (L.) Benth. Ex. Kurz.	Apocynaceae	Shrub	Root, leaves
94	Arandi	*Ricinus communis* L.	Euphorbiaceae	Tree	Seed, root, leaves
95	Kudh	*Saussurea lappa* C. B. Clarke	Asteraceae	Shrub	Bark
96	Kosam	*Schleichera oleosa* (Lour.) Oken	Sapindaceae	Tree	Bark
97	Chitchita	*Sida rhombifolia* Linn.	Malvaceae	Shrub	Root
98	Gulshankhari	*Sida spinosa* L.	Malvaceae	Shrub	Root
99	SafedBhaskatiya	*SolanumTorvum* Sw.	Solanaceae	Shrub	Fruit, flower
100	Kochla	*Strychnos nux-vomica* L.	Loganiaceae	Tree	Root, leaves
101	Ratangauda	*Symplocos racemosa* Roxb.	Symplocaceae	Tree	Bark, root
102	Loung	*Syzygium aromaticum* (L.) Merrill & Perry	Myrtaceae	Tree	Flower
103	Arjun	*Terminalia arjuna* (Roxb. Ex DC.) Wight &Arn.	Combretaceae	Tree	Bark
104	Harra	*Terminalia chebula*Retz.	Combretaceae	Tree	Root, fruit, bark
105	Yellow Kaner	*Thevetia neriifolia* Juss.	Apocynaceae	Tree	Root, fruit, seed
106	Giloy	*Tinospora cordifolia* (Willd.) Miers.	Menispermaceae	Climber	Stem
85	Ajwain	*Trachyspermum ammi* (Linn.)	Apiaceae	Herb	Fruit
107	Bisal Lakruni	*Tridax procumbens* L.	Asteraceae	Herb	Whole plant
108	Methi	*Trigonella foenum-graecum* L.	Fabaceae	Herb	Seed
109	Jangalipyaj	*Urginea indica* (Roxb.) Kunth.	Liliaceae	Herb	Stem
110	Chiraiguda	*Vitex leucoxylon*L. *f.*	Lamiaceae	Tree	Bark, leaves
111	Nirgundi	*Vitex negundo*L.	Lamiaceae	Tree	Root, leaves
112	Ashwagandha	*Withania somnifera* (L.) Dunal	Solanaceae	Shrub	Root
113	Tejbal	*Zanthoxy lumalatum* Roxb.	Rutaceae	Shrub	Seed
114	Adrak	*Zingiber officinale* Roscoe	Zingiberaceae	Herb	Rhizome
115	Ber	*Zizyphus jujuba* Lamk.	Rhamnaceae	Tree	Root

It was a massive task to identify the exact bioactive phytomolecules working against RA. A detailed matrix was constructed and it was revealed that in most of the formulations the bark of *Croton roxburghii* was used.

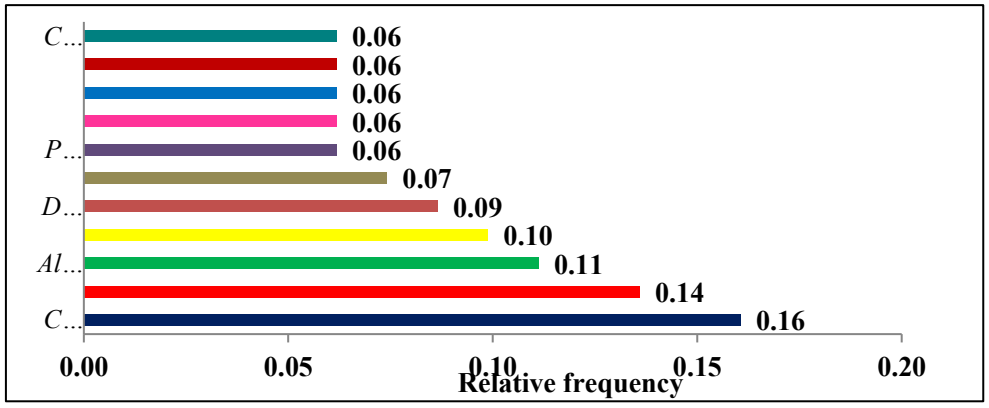

Figure 3. Medicinal plants used for curing RA in polyherbal formulations.

Other frequently used plants were *Datura metel, Allium sativum, Trachyspermum ammi, Dregea volubilis, Asparagus racemosus, Puereria tuberosa, Alstonia scholaris, Madhuca indica, Plumeria acutifolia, Calotropispro cera* in the formulations prepared in diverse media, such as mustard oil, water, jaggery, groundnut oil, clarified butter from cow milk, cow milk, sesame oil and camphor. The mustard oil was the most preferred medium. Powder formulations were in dominant form followed by liniments, solutions and pastes for treatment of RA (Figure 4).

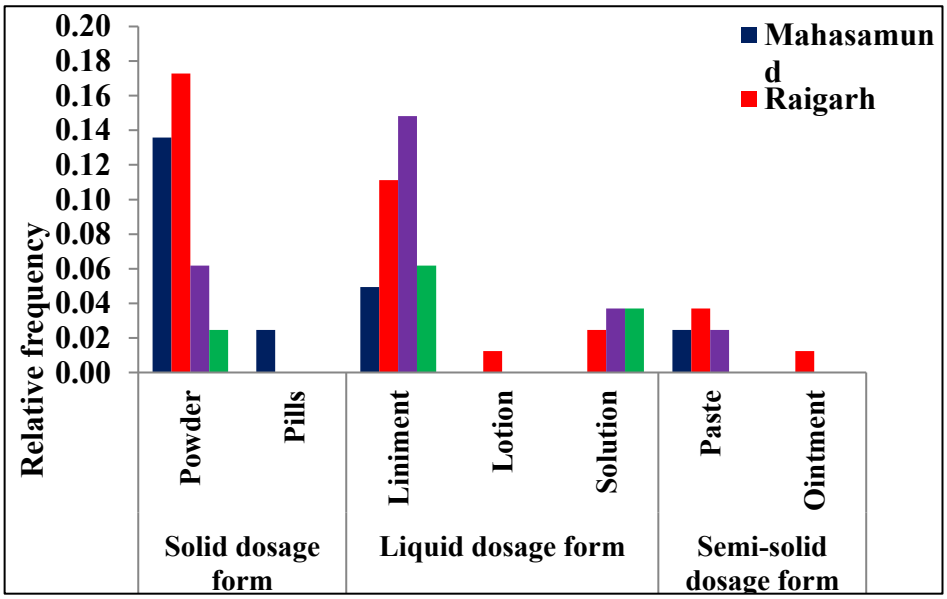

Figure 4. Graphical representation of dosage forms.

Discussion

The measurements of the dosage form were equivocal. Informants generally used cups, finger, teaspoons etc. Different dosage regimens were followed for adults and children. Most of the plant species were not used alone instead they were used together in specific amounts.

Apart from being a vital source of health care, traditional medicine is also an important source of income for many tribal communities and sometimes it is an integral part of a community's identity. Most of the medicinal plants used today are mostly discovered by pre – industrial communities through their observation and experience. At present many communities are involved in the collection, domestication, cultivation and management of medicinal plant resources. The traditional healers use these medicinal plant species collected from the forested areas for the control and cure of RA.

The villagers prefer traditional healers and their prescriptionsfor both diagnosis and prognosis of the disease. Since last few decades there is tremendous reduction in the usage of ethnomedicinal plants owing to increase modern facilities but people still prefer and have faith on herbal formulations for alleviating their ailments.

It is interesting to note that an appreciable section of rural population, particularly study participants, irrespective of their severity of disease status relied on traditional healers and used phytomedicine, also they believe in magico-religious practices and sometimes wear amulet given by traditional healers along with phytomedicines. The study could have been further enriched if studies on the magico-religious practices in the study areas were done.

Large number of human population in villages is dependent upon plant resources for health care. This is due to the fact that allopathic medicines cost high prices and have several adverse effects associated in comparison with herbal medicines. It was also observed that traditional medicinal values are facing challenges owing to the disinterest of youth in learning the traditional knowledge and migration to cities, resulting in decreased transmission of knowledge to younger generation. Therefore, it is utmost important to document the traditional knowledge as it is confined to traditional healers. This will help in carrying out further research work. This is also paramount especially since the native medicinal plants are under immense threats due to global warming, anthropogenic and developmental activities.

Conclusion

The work is currently under progress to pinpoint the exact phytochemical(s) that could be implicated in the process of control and cure of RA. This work is promising and might help in the discovery of potential therapeutic molecule(s) for the control and cure of RA. Traditional healers underlined their well-defined herbal culture and tradition. This may guide for the selection of medicinal plants as potential candidate for curing RA. The herbal claim needs to be exploited further in order to develop new cost-effective drug.

The study depicted that native people prefer traditional medicine due to their socioeconomic status, lack of modern healthcare facilities and inadequate transportation. Resource persons were invariably elderly people of the village. The younger generation being reluctant to take up the practice of herbal healing implies for the documentation of traditional knowledge. It is the only way out to preserve the knowledge base which in turn will conserve the plant resources endemic to the area. The prominent reason for the shortcoming is lack of knowledge about the native plants in relation to their identification, conservation, propagation, associated threats and ethnobotanical uses. The outcome of the present study would be helpful in better understanding the potential of native plants and will also contribute in narrowing the gap in the literature. This comprehensive information will be helpful in great extent to the students, local people, traditional healers, researchers, academicians, conservation professionals and all other stakeholders.

Based on the present study, following recommendations could be made for future study:

1. Incorporation of ethnobotanical knowledge and traditional health care system in school curriculum.
2. Encouragement of research and development for evaluation and standardization of traditional phytomedicines.
3. Establishment of suitable framework and approach for Intellectual Property Rights.
4. Increasing awareness for documentation of ethnobotanical knowledge.

Conflict of Interest

The authors declare that there is no conflict of interest.

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References

1. Akar S, Birlik M, Gurler O, Sari I, Onen F, Manisali M, et al. The prevalence of rheumatoid arthritis in an urban population of Izmir-Turkey. Clinical and Experimental Rheumatology. 2004; 22: 416-420.
2. Hanan MT, Epidemiologic perspectives on women with arthritis: An overview. Arthritis Care Research. 1996.9: 24-34.
3. Malaviya AN, Kapoor SK, Singh RR, Kumar A, Pande I. Prevalence of rheumatoid arthritis in adult Indian population. Rheumatol Int. 1993; 13: 131-134.
4. Chopra A. Disease burden of rheumatic diseases in India: COPCORD perspective (Review). Indian Journal of Rheumatology. 2015; 10: 70-77.
5. Yang CLH, Or TCT, Ho MHK, Lau ASY. Scientific Basis of Botanical Medicine as Alternative Remedies for Rheumatoid Arthritis. Clin. Rev. Allergy Immunol. 2013, 44, 284–300.
6. Smolen JS,Landewe R,Breedveld FC,Buch M,Burmester G,Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. Ann. Rheum. Dis. 2014, 73, 492–509.
7. Dragos D, Gilca M.,Gaman L, Vlad A, Iosif L, Stoian I, et. al. Phytomedicine in Joint Disorders, Nutrients 2017, 9, 70 12 – 18.
8. HyrichKL, Watson KD,Silman AJ,Symmons D.P.M. Predictors of response to anti-TNF-alpha therapy among patients with rheumatoid arthritis: Results from the British Society for Rheumatology Biologics Register. Rheumatology 2006, 45, 1558–1565.
9. Soliman MM,Hyrich KL, Lunt M, Watson KD,Symmons D.P.M., Ashcroft D.M. Effectiveness of rituximab in patients with rheumatoid arthritis: Observational study from the British Society for Rheumatology Biologics Register. J. Rheumatol. 2012, 39, 240–246.
10. Cavalli G,Dinarello CA, Treating rheumatological diseases and co-morbidities with interleukin-1 blocking therapies. Rheumatology 2015, 54, 2134–2144.
11. Hochberg MC, Altman RD, April KT,Benkhalti M.,Guyatt G, McGowan J, et al. American College of Rheumatology, recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. Arthritis Care Res. 2012, 64, 465–474.
12. Nishina, N, Kaneko Y, Kameda H,Kuwana M, Takeuchi T. Reduction of plasma IL-6 but not TNF-alpha by methotrexate in patients with early rheumatoid arthritis: A potential biomarker for radiographic progression. Clin. Rheumatol. 2013, 32, 1661–1666.

13. Abdel-Tawab M,Werz O, Schubert-Zsilavecz M. Boswelliaserrata: An overall assessment of in vitro, preclinical, pharmacokinetic and clinical data. Clin. Pharmacokinet. 2011, 50, 349–369.
14. McAlindon T.E,Bannuru RR, Sullivan MC, Arden, NK,Berenbaum F,Bierma-Zeinstra SM, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. Osteoarthr. Cartil. 2014, 22, 363–388.
15. MatucciA,Cammelli D,Cantini F,Goletti D, Marino V, Milano GM,et al. Influence of anti-TNF immunogenicity on safety in rheumatic disease: A narrative review. Expert Opin. Drug Saf. 2016, 15, 3–10.
16. Cabral VP, Andrade CA,Passos SR, Martins MF,HökerbergYH. Severe infection in patients with rheumatoid arthritis taking anakinra, rituximab, or abatacept: A systematic review of observational studies. Rev. Bras. Reumatol. 2016, 56, 543–550.
17. Mameli A,BarcellonaD, Marongiu F. Fatal Cytopenia Induced by Low-Dose Methotrexate in Elderly with Rheumatoid Arthritis. Identification of Risk Factors. Am. J. Ther. 2017, 24, e106–e107.
18. Rajasekharan S, Pushpangadan P, Biju SD. Folk Medicines of Kerala – A Study on Native Traditional Folk Healing Art and its Practitioners. New Delhi: 1996; Deep Publications, New Delhi (ed. S. K. Jain).
19. Lü S, Wang Q, Li G, Sun S, Guo Y, Kuang H.The treatment of rheumatoid arthritis using Chinese medicinal plants: From pharmacology to potential molecular mechanisms, J Ethnopharmacol. 2015 Dec 24; 176:177-206.
20. World Health Organization, “The Promotion and Development of Traditional Medicine”: Technical Report Series 622, 1978; Geneva.
21. Jain SK, Ethnobotany: Its scope and study. Indian Museum Bull 1967; 2, 39-43.
22. Chhattisgarh VrihadSandarbh, UpkarPrakashan Agra 2002 p3.
23. Chhattisgarh at a Glance, Directorate of Economics and Statistics, Chhattisgarh 2007; p30-31.
24. Pei SJ. Ethnobotanical approaches of traditional medicine studies: Some experiences from Asia. Pharmaceutical Biology2001; 39, 74-79.
25. Akhter E, Bilal S, Haque U. Prevalence of arthritis in India and Pakistan: A review. Rheumatology International 2011, 31(7), 849-855.
26. Jain AK, Patole SN, Less-known medicinal uses of plants among some tribal and rural communities of Pachmarchi forest (M.P.). Ethnobotany 2001; 13, 96-100.
27. Sandhya B, Thomas S, Isabel W, Shenbagarathai R. Ethnomedicinal plants used by the Valaiyan community of Piranmalai Hills, Tamil Nadu, India – A pilot study. African Journal of Traditional, Complementary and Alternative Medicines 2006; 3(1), 101-114.
28. Ignacimuthu S, Ayyanar M, Sankara SK. Ethnobotanical investigations among tribes in Madurai District of Tamil Nadu (India). Journal of Ethnobiology and Ethnomedicine 2006; 2, 25-30.
29. Rajan S, Sethuraman M, Mukherjee PK.Ethnobiology of the Nilgiri Hills, India. Phytotherapy Research 2002, 16, 98-116.
30. Ganesan S, Suresh N, Kesavan L. Ethnomedicinal survey of lower Palani Hills of Tamil Nadu. Indian Journal of Traditional Knowledge 2004, 3(3), 299-304.
31. PushpangadanP, and Atal CK. Ethno-medico-botanical investigations in Kerala - Some primitive tribal of Western Ghats and their herbal medicine. *Journal of Ethnopharmacology* 1984,11(1), 59-77.
32. Ragupathy S, Newmaster SG, Maruthakkutti M, Velusamy B, Ul-Huda M. M. Consensus of the 'Malasars' traditional aboriginal knowledge of medicinal plants in the Velliangiri holy hills, India. *Journal of Ethnobiologyand Ethnomedicine* 2008, 27(4), 8-15.
33. Sharmeen S, Sharmeen T. Traditional Health Practices of Munda Women: Continuity and Change. Man and life 2005, 31 (1&2): 23–36.
34. Shukla R, Chakravarty M. Anthropological Study on Traditional Health Practices of Raj-Gonds, Tribal Health Bulletin, Vol.12 (1&2), 2006: 61–66.
35. Shukla R, Chakravarty M, Gautam MP. Indigenous medicine used for the treatment of Gynecological Disorders by the tribal of Chhattisgarh, India. Journal of Medicinal Plant Research 2008, 2 (12): 356–360.
36. Sonowal CJ, Praharaj P. Tradition vs. Transition: Acceptance of Health Care Systems among the Santhals of Orissa. Studies on Ethno-medicine 2007, 1(2):135–146.
37. Agrawal C, Raghav SK, Gupta B, Das RH, Chaturvedi VP , Goswami K, et al. Tumor necrosis factor-α microsatellite polymorphism association with rheumatoid arthritis in Indian patients. Archives of Medical Research 2005, 36(5), 555-559.
38. Agrawal S, Aggarwal A, Dabadghao S, Naik S, Misra R. Compound heterozygosity of HLA-DR4 and DR1 antigens in Asian Indians increases the risk of extra-articular features in rheumatoid arthritis. British Journal of Rheumatology 1995, 34(1), 41-44.