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A REVIEW OF MEDICINAL PLANTS AS ANALGESICS

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ABSTRACT

Pain is an unpleasant and emotional experience associated with tissue damage. Analgesics are the drugs used to relieve pain. Based on definition of international association of pain study, pain is an undesirable mental and emotional experience that is associated with possible or actual damage of tissue or is created in some periods of these types of pains. It is created by different reasons such as harmful heat, stretch, electrical flow, necrosis, inflammation, laceration and spasm. It is also caused by a wide variety of diseases, surgical interventions and trauma. Degenerative diseases like rheumatoid arthritis, polymyalgia rheumatica, as well as heart, asthma, cancer and inflammatory bowel diseases are also associated with inflammatory processes and pain. It is a complex experience in which cognitive, affective and behavioral features, representing psychological conditions are affected. In most cases, pain is secondary to other complications such as diabetic nephropathy. Pain medication is one of the most common complications managed by the medical practitioners. Recent studies have shown that 22% of primary care patients suffered from pain which persists for more than six months and in some cases the percentage rises to 50% which is related to significant impairment of social functioning and quality of life Classical analgesics of natural origin include opiates and non-steroidal anti-inflammatory drugs but they are associated with side effects such as gastric lesions, hepatotoxicity, renaltoxicity, tolerance and dependence. So, there is a need to explore natural available alternative sources to NSAIDs and opiates. Secondary metabolites of plants such as steroids, flavonoids, alkaloids, terpenoids and glycosides have gained importance due to their diverse pharmacological activities such as anti-inflammatory, analgesic and antipyretic, etc.

KEYWORD: Pain is an unpleasant rheumatica, renaltoxicity, terpenoids and glycosides etc.

INTRODUCTION

Pain is defined as a somatic sensation of acute discomfort, a symptom of some physical hurt or disorder, or even emotional distress. Pain is a crucial aspect of the body's defense mechanisms & it is a part of a rapid warning which relay instruction to the motor neurons of the central nervous system to minimize physical harm.[1]

Pain can be classified into two types: a) Acute pain b) Chronic pain.

a) Acute pain

Acute pain is the body's warning of present damage to tissue or disease. It is often fast and sharp followed by aching pain**.** It is a short-term pain or pain with easily identifiable causes.

b) Chronic Pain

Chronic pain is pain that last much longer than normal pain would with a particular injury. Chronic pain can be constant or intermittent and is generally harder to treat than acute pain. Pain can also be grouped by its source and related pain detecting neurons such as cutaneous pain, somatic pain, visceral pain and neuropathic pain.

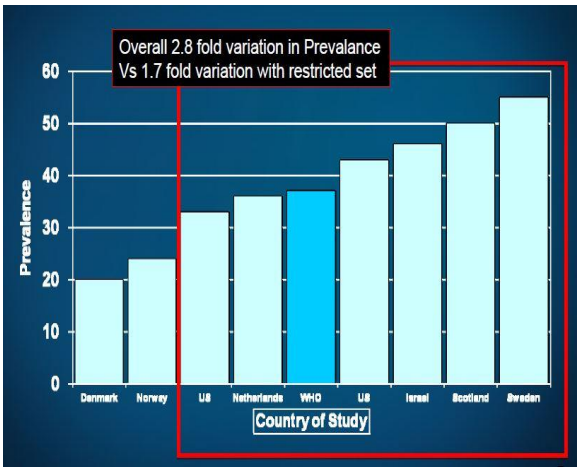
GLOBAL PREVALANCE

Pain is an enormous problem globally. Estimates suggest that 20% of adults suffer from pain globally and 10% are newly diagnosed with chronic pain each year. Nevertheless, the problem of pain has primarily been regarded as a medical problem, and has been little addressed by the field of public health. Globally, it has been estimated that 1 in 5 adults suffer from pain and that another 1 in 10 adults are diagnosed with chronic pain each year.[2] While pain affects all populations, regardless of age, sex, income, race/ethnicity, or geography, it is not distributed equally across the globe. Those who experience pain can experience acute, chronic, or intermittent pain, or a combination of the three. The four largest causes of pain are cancer, osteo- and rheumatoid arthritis, operations and injuries, and spinal problems, making the etiology of pain a complex, transdisciplinary affair. Pain has multiple, serious sequelae including but not limited to depression, inability to work, disrupted social relationships and suicidal thoughts. Of those living with chronic pain, the median time of exposure is 7 years.

LOCATION	PREVALANCE	DURATION > 3MONTHS
Headache	40%	66%
Abdominal	23%	67%
Back	39%	81%
Neck	31%	81%
Shoulder	29%	79%
Hand/wrist	23%	77%
Hip/knee	28%	83%
Ankle/foot	17%	80%

There are multiple reasons regarding pain as a public health priority. The first and foremost is the staggering prevalence of pain. Because pain is a multivalent, dynamic and ambiguous phenomenon, it is notoriously difficult to quantify, and therefore caution is warranted in issuing broad assessments regarding the epidemiology of chronic pain across the globe. 10% of the world's population - approximately 60 million people - endures chronic pain[2] and fairly reliable estimates in individual countries and regions indicate chronic pain prevalence closer to 20-25%.[3,4] Primary care settings in Asia, Africa, Europe, and in the Americas had patients reporting persistent pain prevalence of 10 to 25%. Consistent estimates of chronic pain prevalence in the U.S. range from 12 to 25%, and prevalence of 20% has been noted in Europe.[5,6]

Although there are few estimates of the incidence of global chronic pain, WHO has estimated that as many as 1 in 10 adult individuals are newly diagnosed with chronic pain each year.[2] The prevalence and incidence of chronic pain, both the severity of such pain and the extent of any accompanying disability are also key factors in assessing its burden. The evidence suggests that moderate-to-severe pain is prevalent even in resource-rich settings[7] and that the combination of persistent pain and comorbid psychological disorders produce significant disability across the globe (as measured by impairment of daily activities).



The high prevalence and incidence of global chronic pain, its substantial and growing comorbidities, and its linkage with myriad social and economic determinants collectively provide ample justification for regarding pain as a public health priority. Moreover, there are significant public policy consequences for doing so. Thinking about global chronic pain as a public health priority implies immediately that the global focus on access to essential medicines like opioids is insufficient as a primary policy strategy.

ETIOLOGY

Pain is caused by the stimulation of pain receptors which have free nerve endings.

- Nocireceptors are pain receptors that are located outside the spinal column in the dorsal root ganglion and are named based upon their appearance at their sensory ends. These sensory endings look like the branches of small bushes.
- The perception of pain occurs when these receptors are stimulated and they transmit signal to the central nervous system via sensory neurons in the spinal cord.

PAIN MEDIATORS

High ratio of somatic or visceral pain receptors can be stimulated or sensitized by different stimulants and inflammatory mediators like bradykinin, prostaglandins, leukotrienes, serotonin, histamine, capsaicin and free radicals. The following cases can be mentioned on pain mediators.

➢ Glutamate

Amino acid stimulated by glutamate can perform through ion channels dependent to ligand (glutamate ionotropic receptors) or glutamate metabotropic receptor (mGLuRs) coupled with G protein.[8] Glutamic acid and gamma amino butyric acid (GABA) are respectively two main nervous excitatory and inhibitory transferor of central nervous system in mature mammals. These transferors perform through two metabotropic and ionotropic receptors. Ionoteropic receptors are ligand-gated ion channels that are involved in rapid synaptic transfer while metabotropic receptors belong to big family of G receptors of protein (GPCRs) and committed to control GABA and glutamate. Metabotropic glutamate receptors and metabotropic GABA receptors have play in different levels of pain that control pain transfer.[9] Recently it has been determined that glutamate interferes in transferring sensory input especially during pain transferring.[10]

➢ *Substance P*

Secretion of substance P through axon distributions in skin causes vasodilation, blood capillaries dilation and release of histamine from mast cells. Sensitivity of pain

receptors surrounding surgery place causes secondary through substance P and causes secondary hyperalgesia.[11] Substance P is available inside some primary sensatory neurons that terminate to surface area of dorsal horn of spinal cord. Intensive stimulation of primary afferent fibers distributions that activate A-delta and C-delta fibers, cause secretion of substance P.[12]

- ***Serotonin***

Many neurons in raphe nuclei secrete serotonin as a neurotransmitter. Serotonin can inhibit pain neurons and possibly plays an important role in endogenous anti-pain system. Other neurons of brainstem release epinephrine and norepinephrine in spinal cord. These neurons also inhibit pain neurons.[13]

- ***Histamine***

Histamine has main role in allergic inflammation. Inflammatory responses resulted by histamine release are long and performed by mediator of histamine receptor H1. Antagonists of H1 receptors are usually recognized as antihistamines and have been used to treat allergy for many years. Discovery of histamine four receptors and its expression in different inflammatory cells make it possible to reevaluate histamine functions.[14]

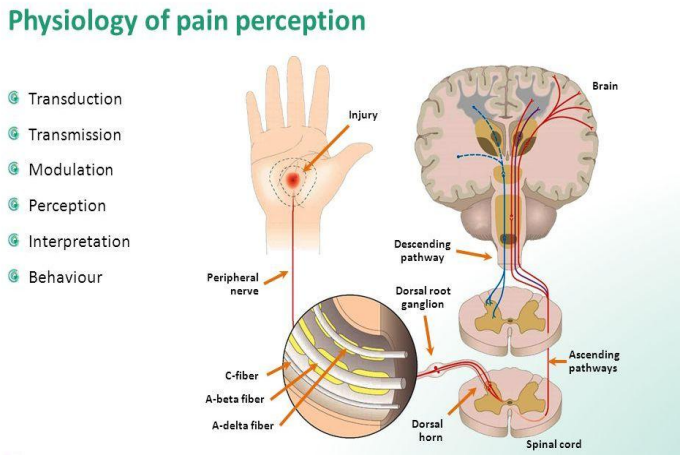
- ***Nervous growth factor (NGF)***

This factor interferes in inflammatory pain directly or indirectly. Inflammatory mediators like cytokines, increases production of NGF in inflamed tissues.[15] NGF stimulates mast cells in releasing of histamine and serotonin. Also this factor can stimulate thermal hyper allergy directly through performing on peripheral terminals of primary afferent fibers.[16] NGF is a member of neurotrophin family and it determines the survival of pain neurons. Recently important role in pain performance has been shown in adults. This factor in skin causes thermal hyper-allergy during a few minutes. Mast cells are the important components action of NGF,[17]

- ***Adenosine and adenosine phosphate***

Inflammation and tissue damage release adenosine and adenosine phosphate [adenosine monophosphate, adenosine diphosphate, adenosine triphosphate (ATP)] and secret into extracellular space and activate pain receptors.[18] ATP receptors are found in primary sensory nerves of dorsal root ganglion and in peripheral nerves. ATP possibly activates pain neurons in healthy skin through P2X2-P2X3 receptors and purinergic P2X3 receptors.

PATHOPHYSIOLOGY OF PAIN



The classic pathway

The pain pathway consists of a three-neuron chain that transmits pain signals from the periphery to the cerebral cortex. The first-order neuron has its cell body in the dorsal root ganglion and two axons, one that projects distally to the tissue it innervates and the other extends centrally to the dorsal horn of the spinal cord. In the dorsal horn, this axon synapses with the second-order neuron, the axon of which crosses the spinal cord through the anterior white commissure and ascends in the spinothalamic tract (STT) to the thalamus. At that site, it synapses with the third-order neuron, which projects through the internal capsule and corona radiata to the postcentral gyrus of the cerebral cortex, where information is somatotopically organized.

The dual pain pathway

In 1920, Henry Head proposed a dual system of afferent fiber projections in the nervous system—an epicritic system that conveys fine tactile sensitivity and discrimination and a protopathic system that participates in sensations produced by nociceptive stimulation. The sensation of pain arrives in the central nervous system by means of two pathways: (1) a sensory discriminative system that encodes the capacity to analyze the nature (for example, burning or pricking), location, intensity, and duration of nociceptive stimulation, subserved by a lateral phylogenically newer system and (2) an affective-motivational component that gives rise to the unpleasant character of painful sensation, subserved by a medial phylogenically older and more primitive system.[19]

These two pathways are in parallel with each other, following the classic three-neuron spinothalamic pathway.

Ascending pathways

Axons of both wide dynamic range (WDR) and noceceptive specific (NS) neurons cross in the anterior white commissure and ascend the spinal cord in the anterolateral quadrant (ALQ).[20,21] The ALQ has two major ascending pain pathways—the STT and the spinoreticular tracts (SRTs). Of the axons ascending to the thalamus, approximately 50% are WDR, 30% are NS, 10% are activated by stimulation of deep tissue, and 2% are exclusively activated by innocuous tactile stimulation1 (Fig. 1).

Nociceptive STT neurons have two main groups of thalamic nuclei: lateral nuclei and medial nuclei. Those axons that project laterally originate in laminae I and V of the dorsal horn, send signals from smaller, more discrete receptive fields in the periphery and are thought to have a role in the discriminative aspects of pain. Those that project medially originate in laminae I, IV and VI, reflect input from large receptive fields, and are implicated in affective-motivational aspects of pain. The medial projections are similar to spinoreticular afférents. Communication between the two groups of thalamic afferents may occur. In addition, the SRT itself projects to the medial thalamus.

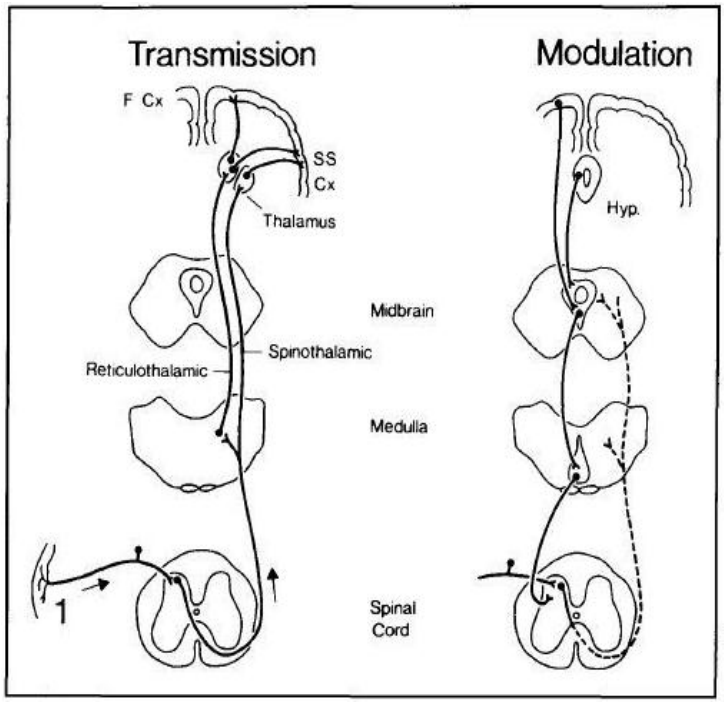


Fig. 1: *Left,* Diagram showing ascending pain pathways

Right, Diagram depicting descending pain pathways. (*FCx:* frontal cortex, *SS Cx:* somatosensory cortex)

The nociceptive SRTs ascend from the dorsal horn through the ALQ to the reticular formation of the brain stem. They are divided into two main groups—the bulbopontine group and the mesencephahc group. The bulbopontine group terminates in a number of nuclei in the pons and medulla. The mesencephahc group projects to the periaqueductal gray (PAG). The reticular formation is a essential to homeostatic and integrative functions of the organism. It has a role in affective-motivational aspects of sensory, motor, and visceral functions. It is the origin of a descending pain-modulating pathway.

Descending pathways

In addition to spinal control mechanisms, nociceptive transmission is under the influence of supraspinal controls.[22] Descending pathways that originate in three major areas the cortex, the thalamus and the brain stem—can modify functions at the spinal level (Fig. 2). Currently recognized transmitters in the descending pathways include epinephrine, norepinephrine, serotonin, and various opioids. Stimulation of sensory and motor cortex can induce inhibitory, excitatory, or mixed effects on both WDR and NS dorsal horn neurons. These effects may be mediated by direct descending fibers or via intermediary brainstem structures.

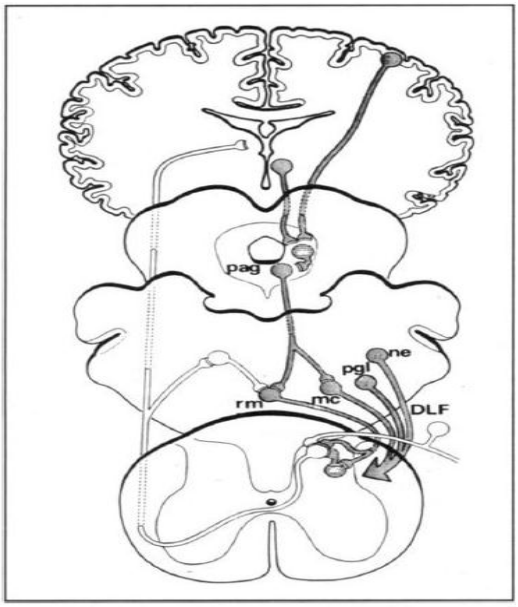


Fig 2: Diagram showing descending pain-modulating pathways in more detail than in Figure 1. Neocortex and hypothalamus project to periaqueductal gray *(pag)*, which, in turn, sends descending projections to nuclei in reticular formation of medulla—medullary nucleus, raphe magnus (rm)-reticularis magnocellularis *(mc)*, nucleus paragigantocellularis *(pgl)*, and noradrenergic medullary cell groups *(ne)*. These nuclei, in turn, project through dorsolateral funiculus *(DLF)* to dorsal horn of spinal cord.

Analgesia: Analgesia simply means the absence of pain without losing consciousness.

Mechanism of action of Analgesics: The analgesia system is mediated by 3 major components:

- The periaquaductal grey matter (in the midbrain).
- The nucleus raphe magnus (in the medulla).
- The pain inhibitory neurons (within the dorsal horns of the spinal cord).

Pain and discomfort in everyday life are often treated with over-the-counter (OTC) analgesic medications. These drugs are remarkably safe, but serious side effects can occur. Up to 70% of the population in Western countries uses analgesics regularly, primarily for headaches, other specific pains and febrile illness. But it is not known whether the patterns of use are consistent with good pain management practices. OTC analgesics are also widely used to treat dysphoric mood states and sleep disturbances, and high levels of OTC analgesic medication use are associated with psychiatric illness, particularly depressive symptoms, and the use of alcohol, nicotine and caffeine. For example more than 4 g per day of acetylsalicylic acid (ASA) or acetaminophen over long periods is considered abuse. Here people using excessive amounts of OTC analgesics may need more effective treatments for chronic pain, depression or dysthymia.[23]

While in choosing analgesics, the severity and response to other medication determines the choice of agent; the World Health Organization (WHO) pain ladder[24] specifies mild analgesics as its first step.

Analgesic ladder was created by the World Health Organization (WHO) as a guideline for the use of drugs in the management of pain. Originally published in 1986 for the management of cancer pain, it is now widely used by medical professionals for the management of all types of pain.

The general principle is to start with first step drugs, and then to climb the ladder if pain is still present. The medications range from common, over-the-counter drugs at the lowest rung, to strong opioids.

The WHO guidelines recommend prompt oral administration of drugs ("by the mouth") when pain occurs, starting, if the patient is not in severe pain, with non-opioid drugs such as paracetamol (acetaminophen) or non-steroidal anti-inflammatory drugs (NSAIDs) including COX-2 inhibitors. Then, if complete pain relief is not achieved or disease progression necessitates more aggressive treatment, a weak opioid such as codeine, dihydrocodeine or tramadol is added to the existing non-opioid regime. If this is or becomes insufficient, a weak opioid is replaced by a strong opioid, such as morphine, diamorphine, fentanyl, buprenorphine, oxymorphone, oxycodone, or hydromorphone, while continuing the non-opioid therapy, escalating opioid dose until the patient is pain free or at the maximum possible relief without intolerable side effects. If the initial presentation is severe pain, this stepping process should be skipped and a strong opioid should be started immediately in combination with a non-opioid analgesic.[25]

WHO Pain Ladder

Step 1.	Mild pain:			Non-opioid	+	Optional adjuvant	If pain persists or increases, go to step 2.
Step 2.	Moderate pain:	Weak opioid	+	Non-opioid	+	Optional adjuvant	If pain persists or increases, go to step 3.
Step 3.	Severe pain:	Strong opioid	+	Non-opioid	+	Optional adjuvant	Freedom from pain.

Generally analgesic agents are classified as,

- **Non opioids**

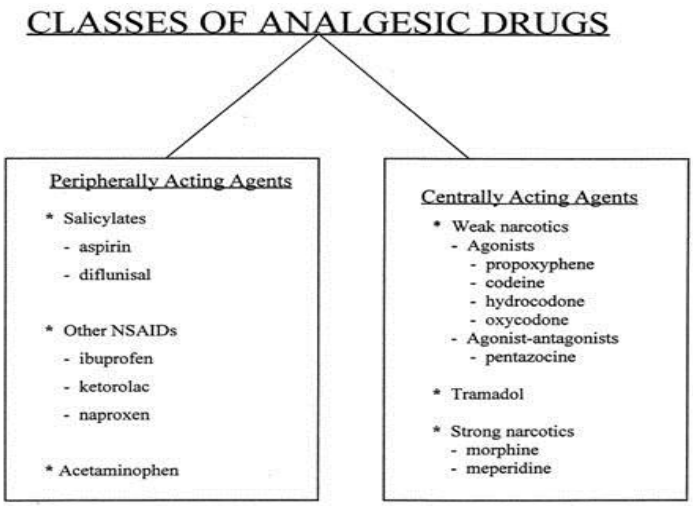
NSAIDs are used as non opioid analgesic agents.
Paracetamol, aspirin, nimesulide, ibuprofen, ketorolac.

- **Opioids**

Morphine, pethedine, codeine, tramadol.

- **Alcohols**

Ethanol



SIGNFICANCE OF HERBS IN PAIN

Recent studies have shown that 22% of primary care patients suffered from pain which persists for more than six months and in some cases the percentage rises to 50% which is related to significant impairment of social functioning and quality of life.[26] Although pain mainly is considered as a defense mechanism which is created when a tissue is damaged and caused a person show reaction and remove pain stimulant,[27] however, in sever condition it impairs social functioning and reduces quality of life.[28]

The human body's natural response to injury results in inflammation-induced pain, swelling, and erythema. In order to reduce pain, anti-inflammatory agents such as NSAIDs act on the multiple inflammatory pathways, which, although often very effective, can have undesirable side effects. The use of non-steroidal anti-inflammatory drug (NSAID) medication is still the mainstay of most classically taught clinicians for joint and spine related inflammatory pain, despite their commonly known side effects.

Side effects of steroid-based medications	
Increased risk of infection	Impaired wound healing
Dermatitis	Increased appetite
Fluid retention edema	Weight gain
Fat deposits in face, chest, upper back and stomach	Worsening of previously acquired medical conditions
Mood change	Depression
Hypertension	Hyperglycemia
Cushingoid-like state	Adrenal suppression and crisis
Stomach ulcers	Cataracts
Osteoporosis	

Millions of people suffering from different types of damage who wish to find a drug with less side effects.[29] Medicinal plants have been suggested for prevention or treatment of pain related conditions. Drugs with herbal origin have attracted attention of researchers and people by having low or no side effects.[30,31]

Table: Some plants having analgesic activity.

Sl.no.	Common name	Botanical name	Family	Plant part used
1.	Euphorbia	Euphorbia fusiformis	Euphorbiaceae	Roots
3.	Balsam Fir	Abies balsamea	Pinaceae	Bark
4.	Coriander	Coriandrum sativum	Apiaceae	Seeds and leaves
5.	Black pepper	Piper nigrum	Piperaceae	Fruit
6.	Curry leaf	Murraya koenigii	Rutaceae	Leaves
7.	Bariara	Sida acuta	Malvaceae	whole plant
8.	Cluster Fig Tree	Ficus glomerata	Moraceae	Bark and leaves
9.	China rose	Hibiscus rosa sinensis	Malvaceae	Leaves
10.	Vilayati mehndi	Myrtus communis	Myrtaceae	leaves
11.	Orange jasmine	Murraya paniculata	Rutaceae	Bark
12.	Kadam	Mitragyna parvifolia	Rubiaceae	Fruits
13.	Palash	Butea monosperma	Fabaceae	Leaves
14.	Jangli badam	Sterculia foetida	Sterculiaceae	Seeds
15.	Sprengel	Mikania glomerata	Asteraceae	Leaves
16.	Globe artichoke	Cynara scolymus	Asteraceae	Leaves
17.	Elephant foot	Elephantopus scaber	Asteraceae	Leaves
18.	Lemon eucalyptus	Eucalyptus citriodora	Myrtaceae	Essestial oil
19.	Mart	Trianosperma tayaya	Curcurbitaceae	Root
20.	Wild coffee	Casearia sylvestris	Flacurteaceae	Leaves and bark

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