

The Janus Corner



This occasional section within the journal surveys visions and achievements, often not on the main track of the developing biomedical sciences, but all relating to discoveries and developments of medicinal – both ancient and modern. What they have in common, in one way or another, is providing further background and glances around the edges of the core discipline of pharmacognosy, as it has been and continues to evolve within our times.

An Opinion: Herbal Medicines may Provide a Means of Controlling the Covid-19 Pandemic

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Since the onset of the current Covid-19 pandemic, the search has been on for methods to provide immunity, decrease mortality and lessen the symptoms of the disease. Much of the current research focuses is on the development of effective vaccines and with good reason. The discovery of an effective vaccine promises the establishment of widespread immunity to the SARS-COV-2 virus and is potentially the best long-term strategy to obtain herd immunity and thereby control this disease. However, the production an effective vaccine may take years and strains of the virus resistant to the vaccine are likely to have developed during that period, lessening the efficacy of the vaccine. Medical science must also look at other options to treat this disease, at least in the interim and potentially as an adjunct to vaccines once developed. Herbal medicines may provide effective therapies with multiple beneficial effects against Covid-19 and these should be explored. Individual medicines may inactivate the virus, block its reproduction or spread, or decrease the symptoms, thereby not only lessening suffering and decreasing mortality, but also lessening further spread. Indeed, several groups have already highlighted the potential of selected herbal medicines against this virus. For example, Thailand Medical News published a report in January 2020 highlighting *Glycyrrhiza glabra* (liccorice) as a potential therapy for covid-19 based on its previous efficacy against the SARS epidemic of 2003.¹ Furthermore, several Chinese studies tested selected Traditional Chinese Medicines (TCM) against covid-19 and reported that some TCMs reduced the symptoms of the disease, especially fevers and decreased the viral load substantially.² Based on that report, four TCMs were highlighted as having the greatest potential: Qingfei Paidu decoction, Gancaoganjiang decoction, Sheganmahuang decoction and the Qingfei Touxie Fuzheng decoction. Interestingly, liccorice was a major component of all of those therapies, further highlighting its potential as a Covid-19 therapy.

Other plants may also have potential and they should not be overlooked in future research. However, given the high number of mortalities already caused by Covid-19 and the urgency to discover effective treatments, it is important to narrow the focus of promising plants to screen for activity against this disease. In the remainder of this discussion, I wish to highlight the potential of an Australian plant species (*Terminalia ferdinandiana* Exell., commonly known as Kakadu plum). Before exploring the potential of this species, it is prudent to discuss the disease onset and progression, as well as its symptoms and stages, thereby highlighting therapeutic targets.

The latest identified novel Coronavirus (SARS-CoV-2) that causes Covid-19 comes from a family of viruses that cause respiratory illnesses. Most Coronaviruses are relatively benign and many cause symptoms that we know as the 'cold'. However, some Coronaviruses (notably SARS and MERS) are particularly worrisome as they are both highly infectious as well as being highly virulent. The recent emerging strain SARS-CoV-2, shares some features in common with the previous SARS and MERS epidemics. SARS-CoV-2 is highly infectious and is readily spread by both airborne transmission and by contact with contaminated individuals and surfaces. SARS-CoV-2 has also caused a high level of mortality, yet generally not to the same % of infected people as seen during the previous SARS and MERS epidemics. Indeed, whilst the mortality rate as a percentage of overall infections globally is higher than that of a seasonal influenza strain, it is considerably less than either SARS or MERS. Furthermore, a high percentage of SARS-CoV-2 infected individuals remain asymptomatic (estimates range from 10-90% of infected individuals) and are unaccounted for in the infection statistics. Therefore, the actual mortality rate per number infected may be substantially lower than is currently reported. However, despite

the lower mortality rate compared to the previous SARS and MERS infections, the high infection rate of SARS-CoV-2 still results in high numbers of overall mortalities, making Covid-19 of considerable concern. Important points of note regarding SARS-CoV-2 infections and Covid-19 include:

1. SARS-CoV-2 is relatively benign in most otherwise healthy individuals. Young, healthy people have substantially lower risks of mortality or severe morbidity from SARS-CoV-2 infections than older people do. Indeed, most develop symptoms similar to a common cold, or in some cases, an influenza infection. Indeed, a substantial percentage will remain asymptomatic. The vast majority of this group recover fully in a similar period to the common cold. However, all infected individuals, including asymptomatic people, are contagious from before symptoms appear (if they do) until the virus has cleared from them. Social distancing and increased hygiene vigilance are useful in reducing the spread from these people. It is likely that these individuals will have acquired immunity to SARS-CoV-2 following the initial exposure and will not re-catch the disease following further exposure, although this is yet to be verified.

2. Covid-19 is of substantially greater concern in vulnerable groups including older people (generally >70 years of age), immunocompromised people, including individuals with immune disorders, individuals on cancer therapies or intensive antibiotic or immune suppression therapies (such as after transplantation procedures), people with high blood pressure or diabetes mellitus, or individuals with other chronic or acute respiratory illnesses. Individuals in these categories constitute the vast majority of mortalities attributed to Covid-19. Indeed, all available statistics report that the vast majority of deaths occur in individuals over 70 years of age with other serious morbidities unrelated to Covid-19.

3. In many cases, Covid-19 mortalities result from over-activity of the immune system, resulting in an increased inflammatory response described as a “cytokine storm”. In older and immunocompromised individuals, this can result in viral pneumonia (alveoli fill with fluid) making breathing difficult. This can overwhelm the ability of the lungs to exchange oxygen, especially in people with other underlying respiratory illnesses. Covid-19 can also put added stress on the heart and may result in heart attack in some people (particularly older people and/or individuals with high blood pressure).

4. In some individuals, covid-19 may not directly cause mortality, but instead may render the infected person more susceptible to secondary infections including influenza, colds and bacterial pneumonia. These secondary infections cause many of the mortalities recorded globally. This is not only of concern to individuals in the vulnerable groups and these secondary infections are also of concern to young otherwise healthy individuals. These pathogens can quickly establish secondary infections in the lungs and can rapidly cause pneumonia and other respiratory diseases, putting increased burden on respiration and on the individual's immune system. Bacterial pneumonia and other non-Covid-19 bronchial conditions may subsequently be responsible for much of the mortality recorded globally.

5. Unfortunately, the incidence of the other secondary infections increases substantially in the colder winter months when people shelter inside for warmth, at a period also corresponding to greater SARS-CoV-2 transmutability. This may contribute to the substantially higher mortality rates recorded to date in northern hemisphere regions such as China, Iran, Italy, Spain and the USA, compared to southern hemisphere regions such as Australia, South Africa etc. It is hoped the transmission rate (and thus the number of fatalities) will decrease substantially in the affected northern hemisphere regions as the weather warms. Conversely, the rate of transmission (of both Covid-19 and of secondary infections) is likely to increase in the southern hemisphere in coming months in the absence of other measures such as social distancing.

It is evident from the above points that there are a number of strategies to control the spread of the virus and perhaps more importantly in the short term, to decrease the mortality rates in affected people (particularly those in the vulnerable categories). The first of these is behavioural modification. Many countries globally have already instigated a form of social isolation, whether that be via the banning of congregating in public and the closure of businesses such as cafes, restaurants, hotels and bars etc. in countries such as Australia, or via the more stringent community lockdowns in countries such as China, Italy and some states of the USA. All affected countries are also requiring their citizens to maintain a distance between themselves and others when it is necessary that they are in public. Practicing increased hygiene vigilance and the frequent use of hand sanitisers has also been adopted in affected areas, with the aim of decreasing infection rates. All of these measures aim to slow the rates of infection to allow medical facilities to cope with the increased burden. However, they will not stop the disease or its ultimate spread. To achieve that, a form of herd immunity is required. Ideally, that will be through the development of an effective SARS-CoV-2 vaccine. Unfortunately, most experts estimate that the development and wide scale production of a vaccine is still at least 12-18 months away. Many experts estimate that by that time, many regions globally may have already acquired herd immunity through the high numbers of SARS-CoV-2 infections that will happen naturally through community acquired infections. Therefore, in many people (particularly young and healthy people) acquiring the infection may have positive effects in the long-term, both to the individual and to the greater population. Currently, most countries strategies aim to lessen the burden on the medical system, by spreading the rate of infection over a greater time.

Other measures are also possible in people who have acquired Covid-19 to lessen the symptoms, thereby also decreasing both the mortality rate and period of time that the infected person is contagious (thus further decreasing the spread). Currently, medical science is attempting to “repurpose” several drugs previously indicated for other purposes (e.g. chloroquine). However, traditional and herbal medicines also hold great promise as potential therapies to decrease the symptoms of Covid-19, thereby saving lives. *Terminalia ferdinandiana* Exell (commonly known as Kakadu plum) has good potential in this area:

1. Kakadu plum extracts contain extremely high antioxidant contents, including the highest natural source of ascorbic acid of any plant globally. Indeed, they contain ~900 times (g/g) the ascorbic acid content to blueberries. High ascorbic acid levels enhance the immune system, thereby decreasing the likelihood of acquiring a SARS-CoV-2 infection. Kakadu plum extracts also contain other compounds that are known to stimulate the immune system and preliminary data has shown that the extracts are good immuno-stimulants. All this may result in lower incidences of developing Covid-19, even in individuals infected with SARS-CoV-2. Furthermore, the symptoms and thus the mortality and transmissibility, would also be decreased.

2. The extract may also block SARS-CoV-2 viral replication, although this is yet to be verified. Recent studies (in preparation) have demonstrated that Kakadu plum extracts inhibit 3 stages of HIV-1 replication (viral entry into the cell, HIV-1 reverse transcriptase activity and HIV-1 protease activity), making it particularly useful as a HIV-1 therapy. Indeed, crude Kakadu plum extracts have similar anti-HIV-1 activity to the current regimen of anti-retroviral drugs. Notably, a current strategy for controlling Covid-19 involves human trials of previously used HIV anti-retroviral drugs. Thus, Kakadu plum extracts may also be a good candidate for further trials. Additionally, Kakadu plum extracts have also been shown to be potent inhibitors of Dengue virus (in preparation). Whilst we don't yet completely understand the mechanism by which Kakadu plum inhibits Dengue virus replication, preliminary studies

have already demonstrated that it inhibits the entry of the virus into the cell (as it also does for HIV). This is particularly noteworthy as blocking cell entry would not only treat Covid-19 once the SARS-CoV-2 has infected an individual, it may also block an individual acquiring an infection, even when exposed to the virus. Furthermore, like HIV and Dengue virus, SARS-CoV-2 is an RNA virus. As studies have shown that Kakadu plum inhibits several viral reverse transcriptase enzymes, it is possible that it may have similar effects against SARS-CoV-2. No studies have yet verified the potential of Kakadu plum extracts against SARS-CoV-2 replication because of the fast pace of this pandemic. However, Kakadu plum extracts are promising antiviral therapies and this should be further explored.

3. Kakadu plum therapy may also decrease many of the serious symptoms associated with Covid-19. As noted above, much of the mortality associated with Covid-19 is related to the induction of cells to release pro-inflammatory cytokines, resulting in a “cytokine storm” and the associated inflammation. Notably, several studies have shown that Kakadu plum extracts inhibit the release of pro-inflammatory cytokines and the same time stimulates the release of anti-inflammatory cytokines. To date, only *in vitro* studies have been reported and *in vivo* testing is required. However, given the mechanisms by which the extracts work, it is highly likely that they may have profound effects on inflammation in infected people, thereby decreasing breathing difficulty, potentially saving lives.

4. Kakadu plum extracts are also likely to decrease the incidence and

severity of secondary infections, particularly by pneumonia causing bacterial pathogens. As these infections are a common cause of mortality in individuals with Covid-19, it is likely that this may also save further lives. Notably, secondary infections not only affect individuals in the vulnerable groups, but also affect younger, healthy individuals. Therefore, potent broad-spectrum antibacterial activity would be beneficial to all members of society. Multiple recent studies have reported that Kakadu plum extracts are highly potent inhibitors of many bacteria, including bacterial causes of pneumonia, as well as highly resistant bacterial strains. The above benefits have focussed on inhibiting the incidence of Covid-19 in people and on its treatment once Covid-19 is established. However, other potential benefits of Kakadu plum extracts are also obvious. Given the antiviral and antibacterial activities discussed above, it may also be particularly useful as a surface cleaner and disinfectant and as a component of personal hygiene products such as soaps and hand sanitisers. In summary, Kakadu plum extracts have substantial potential in the control and treatment of Covid-19 and it much more study into the anti-covid-19 properties of this plant is warranted.

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