

## Review Article

## The efforts on using various agricultural substances, proteins or products for the purpose of pleurodesis

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**Abstract:** There are a great number of substances and products all over the world, used for pleurodesis. However, either the pleurodesis successes of these agents are not at the desired level or they reveal various side effects after usage. In addition, the pleurodesis processes performed with these agents could be expensive, which makes it a negative influence for many patients in many countries. In this context, new herbal-originated pleurodesis substances are investigated by using various agricultural originated substances, proteins or products. In this review, the results of previously conducted studies of pleurodesis processes with herbal-originated substances, animal proteins or commercially available products of agricultural science, have been collected. These applications, which may be defined as phyto therapeutic pleurodesis, intensify mostly on viscum album (mistletoe) pleurodesis, and the copaifera multijuga, brucea javanica, sericin, and olive oil pleurodesis processes follow this.

**Keywords:** Pleurodesis, Phyto therapeutic, Agriculture, Viscum album, Mistletoe, Sericin, Copaiba oil, Olive oil, Copaifera multijuga, Brucea javanica

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**INTRODUCTION:**

When air or liquid accumulates in the pleural space, the first process is the evacuation of the accumulated air or liquid, in the treatment algorithm. Although several methods like chest tube thoracostomy, small caliber catheter thoracostomy, indwelling pleural catheter, pig-tail catheter, and tunneled pleural catheter have been developed for this purpose, a pleurodesis process is frequently added to the treatment, to avoid the recurrence of the pathology.

Pleurodesis is the induction of symphysis between the visceral and parietal pleura to obliterate the pleural space for preventing the accumulation of either air or liquid [1, 2]. This procedure is performed to treat various kinds of primary or recurrent lung pathologies such as malignant, exudative and/or recurrent pleural effusions; primary, secondary and/or recurrent pneumothorax, and hepatic hydrothorax [3-5]. Many substances have been used for pleurodesis process; however, there is no agent on which a wide-held consensus was obtained. An ideal pleurodesis agent must be safe, widely available, inexpensive, and easily administrated. The literature describes various kinds of

pleural sclerosant agents; however, most of them have different types of adverse effects. On the other hand, the cost profile of pleurodesis agents is another debatable point; inexpensive agents are necessary.

Therefore it is clear that there is a need for new pleurodesis agents with low cost-profile and fewer side effects, but with high efficiency and cost-effectiveness. It is reviewed from literature that various researchers have tried to use some substances, proteins or products, which are frequently mentioned by agricultural scientists, for the success of pleurodesis. The purposes of these studies are trying to develop new pleurodesis agents with high efficiency, low cost-profile, and fewer side effects, and present them to daily practices. For this purpose, it is understood in the literature that viscum album (mistletoe) extract, copaifera multijuga oil, olive oil, brucea javanica oil emulsion, and sericin protein have been used. The purpose of this review is to reveal the aims of these studies that were conducted for “alternative pleurodesis practices”, collect these studies together, emphasize similar points in them, and set targets for future studies.

### 1.The Most Commonly Preferred Agents of Pleurodesis:

Many substances, solutions, agents or products from talcum powder to silver nitrate, from various antibiotics to antineoplastic medications, have been used for the purpose of pleurodesis. In the light of the up-to-date literature review, the most-frequently used agents were talcum powder, doxycycline, silver nitrate, iodo povidone, autologous blood, dextrose solution, bleomycin, tetracycline, quinacrine, doxorubicin, erythromycin, ethanol, polidocanol, mitoxantrone, and OK-432. Although many pleurodesis agents are used, the most-frequently used one in the world, in a widespread geographical area, is the talcum powder.

#### a.Talcum powder pleurodesis

Talc is a powder of *hydrous magnesium silicate* containing various contaminants that has been shown to be effective in treating malignant pleural effusions and spontaneous pneumothorax. Commercially available purified talc is free of asbestos and is considered safe for therapeutic use. Talcum powder pleurodesis was first described by Bethune in 1935, and has been used clinically since 1953 to treat and prevent pneumothorax [6, 7]. In literature, many studies describe the effectiveness of talc pleurodesis in malignant pleural effusions, exudative pleural effusions or recurrent effusions, as well as in spontaneous pneumothorax cases [8-10]. There are several series on the literature claiming that using talcum powder is highly safe, does not have any complications or the complications are not related with talc pleurodesis [11,12]. However, some patients developed adverse reactions associated with talcum powder pleurodesis such as fever, pleuritic chest pain, tachycardia, dyspnea, hypotension, pulmonary edema, and pulmonary emboli. It has also been reported that the shortness of breath is severe in some patients with a need of mechanical ventilation. Moreover, some patients developed foreign body reactions such as talcoma and talc granulomatosis.

Brant *et al.*; performed 33 talcum powder pleurodesis on 29 patients and reported the highest rate of complications (51.7%) after pleurodesis [13]. In their series, complications were categorized as major and minor complications, and observed in 15 patients [13]. The minor complications included tachycardia (n=11; 33.3%), chest pain (n=9; 27.3%), fever (n=8; 24.3%), and dyspnea (n=4; 12.1%); whereas, seven patients (24.1%) suffered from major complications such as severe hypoxemia and hypotension [13]. Two of these complicated patients died, and one death was directly attributed to adult respiratory distress syndrome

(ARDS), the other was hastened by a talc pleurodesis-related tachycardia [13].

Rehse and colleagues reported one of the highest ratios (33%) of respiratory complications after talcum powder pleurodesis [14]. They performed 89 talc pleurodesis in 78 patients; 19 (21.3%) of the cases involved only minor complications, including fever (n=13, 14.6%), asymptomatic hypoxemia (n=9, 10.1%), dyspnea and oxygen requirement (n=6, 6.7%), increased the need for narcotics (n=5, 5.6%), while subcutaneous emphysema, local infection, and asymptomatic hypotension occurred after one procedure (1.1%) [14]. However, 11 patients (12.3%) had major complications including pulmonary edema (n=11, 12.3%), ARDS (n=7, 7.9%), pulmonary embolism (n=1, 1.1%), and one patient (1.1%) died within 24 hours after bilateral talcum powder pleurodesis [14].

Gonzalez *et al.*; also reported the adverse effects of thoracoscopic talcum powder insufflations; in their study, of 138 patients that underwent 142 procedures, the most commonly observed side effect was dyspnea (n=12, 8.7%), followed by talc-related lung injury (n=4, 2.9%), and respiratory deterioration (n=4, 2.9%) [1]. Pulmonary edema, cough, somnolence, restlessness, oxygen desaturation, and deterioration were the other presentations; six patients (4.4%) required non-invasive mechanical ventilation (NIMV) or mechanical ventilation, one patient (0.7%) on NIMV deceased due to a possible talc reaction [1].

There are several studies in the literature reporting that talcum powder pleurodesis causes inflammatory reactions. Caesar *et al.*; published a case report and described an eosinophilic cholecystitis case, three weeks after administration of talc slurry pleurodesis for secondary pneumothorax [15]. Considering the extensive surface area of the pleural cavity and abundance of lymphatic and vascular vessels, the hypothesis that talc particle migration plays a role in the genesis of systemic effects should be considered. According to Caesar *et al.*; talcum powder pleurodesis has been shown to cause an acute systemic response, including an increase in serum IL-8, a potent mediator of eosinophile chemotaxis [15]. Not only the serum IL-8 level and eosinophilic chemotaxy, overall white blood cell count, percentage of neutrophils, C-reactive protein levels, and body temperature were significantly increased; however, the percentage of lymphocytes was significantly decreased in the talcum powder pleurodesis group according to Froudarakis and colleagues [16]. In another study, Arellano-Orden *et al.* studied the survival and inflammatory effects between

small particle-size talcum powder and large particle-size talcum powder groups. The patients, who received small particle-size talcum powder, had significantly higher pro-inflammatory cytokine levels such as IL-8, tumor necrosis factor alpha, vascular endothelial growth factor, and basic fibroblastic growth factor in the pleural fluid and serum, while having a high mortality rate [17].

It has also been reported in the literature that after talcum powder pleurodesis, there might be several changes in the radio-diagnostic findings, and some other changes like talcoma, talc granulomatosis might also be observed, and there might also be false positivity according to positron emission tomography (PET-CT) findings [7,18,19]. Ergonul *et al.* reported a talc granulomatosis inflammation after a talcum powder pleurodesis [18]. Ocak *et al.*; published a case report with a pleural mass after eight years onset of a talcum powder pleurodesis and after surgical excision of the mass, a talcoma was demonstrated by chronic pleuritis, calcifications, and a foreign body giant cell reaction [19]. The talc deposits, talcoma, and talc granulomatosis subjects could be a false-positivity on PET-CT. Vandemoortele *et al.*; reported an increased flouro-deoxyglucose (FDG) uptake in the areas of talc deposits, and suggested advanced diagnostic tools for the patients with a history of asbestosis exposure in order to exclude malignant mesothelioma [7]. They realized talcum powder pleurodesis induces a granulomatous reaction even 20 years later from administration, and had a high value of maximum standardized uptake value ( $SU_{vmax}$ ) which complicates differential diagnosis [7].

These complication rates, wide range of complications, systemic inflammatory reactions, and undesired radiological findings after talcum powder pleurodesis challenge the assumption that talcum powder pleurodesis is a safe procedure. There were a significant number of serious complications, including ARDS, hypoxia and dyspnea required NIMV and mechanical ventilation, serious cardiac problems such as tachycardia and hypotension, and even death were reported.

#### **b. Doxycycline pleurodesis**

Doxycycline is another agent is being administrated through intrapleural to achieve pleurodesis. The molecule is actually an antibiotic and the metabolism of this drug is in the liver, and excretion is from urinary system. It has been reported in the studies that liver toxicity may be observed after intrapleural application, since the metabolism is from the liver [20]. Mitchem *et al.*; reported a comparative

study of doxycycline and talcum powder pleurodesis, the preferred animal was rabbits [20]. In the doxycycline pleurodesis group, elevated liver function enzymes were observed, liver tissue toxicity was detected such as fatty infiltration of hepatocytes, and numerous amounts of nuclei were psychotic [20]. Trichrome staining evidenced a moderate increase of collagen fibers, especially in the peri-portal spaces [20]. In another comparative study of doxycycline pleurodesis versus talcum powder, erythromycin, and diazepam pleurodesis, published by Miller *et al.*, there was a trend to higher mortality in the doxycycline treated animals [21]. They mentioned that although doxycycline pleurodesis group had a high response rate of induced pleural adhesions, it was also associated with severe inflammatory reactions [21]. In this study, doxycycline pleurodesis group had eight rabbits, three of them died before the end of study, yielding a 38% of mortality rate [21]. The necropsy of the animals revealed severe inflammatory reactions involving the underlying lung, pericardium, and mediastinum without gross evidence of hemothorax [21]. However, Guo *et al.*; reported another rabbit study and presented hemothorax adverse effect after doxycycline pleurodesis [22]. According to gross examinations of the sacrificed animals, two (28.6%) of seven rabbits had hemothorax [22].

Abouzgheib *et al.*; reviewed the efficacy rates and complication rates after administration of 500 mg doxycycline pleurodesis in humans [23]. In different case series, the efficacy rate of doxycycline pleurodesis ranges between 61-81%; however, chest pain complication ranges between 22-97%, and detected fever ranges between 3-22% of the patients [23]. Therefore, doxycycline pleurodesis also have some complications included liver toxicity, inflammatory reactions, chest pain, fever, and hemothorax.

#### **c. Silver nitrate pleurodesis**

Silver nitrate is an inorganic compound with a formula of  $AgNO_3$  and has been used in pleurodesis for many years. Although there are different practice doses in the literature, silver nitrate pleurodesis also have various side effects, similar to other pleurodesis agents. In a research, Terra *et al.*; reported pleurodesis results with three different doses of silver nitrate in patients with malignant pleural effusion [24]. The study included 60 patients and 199 adverse events were observed, including 23 serious adverse effects [24]. The most frequent serious side effect was hypoxia. One patient developed severe hypoxia two days after pleurodesis, ARDS was diagnosed, and the patient was intubated and remained under mechanical ventilation;

subsequently recovered after this period [24]. Twelve patients had hypoxia, started 24h after pleurodesis and were managed with nasal oxygen catheter [24]. Unfortunately, one patient died and it was possibly related to pleurodesis [24]. Other side effects that observed after silver nitrate pleurodesis were as follows: acute kidney injury, elevated serum creatinine level, anemia, elevated leukocyte count and CRP levels, chest pain, elevated liver enzymes, nausea, vomiting, embolic events, tachycardia, confusion, and imbalance of different electrolytes [24].

Beside this research, there are several other studies revealed the side effects of silver nitrate pleurodesis. Menna *et al.* reported the efficiency of silver nitrate pleurodesis after failed talcum powder pleurodesis [25]. However, of the 29 patients who received silver nitrate, five cases (17.2%) developed fever [25]. Similarly, in another study published by Terra *et al.*; silver nitrate pleurodesis was administered to 63 patients for the treatment of malignant pleural effusions [26]. They performed 70 silver nitrate pleurodesis with several adverse effects including; pain (n=7, 10.0%), infection (n=2, 2.9%), and fever (n=1, 1.4%) [26].

There are some animal studies in the literature reporting hemothorax complication was observed, after silver nitrate pleurodesis. Vargas *et al.*; randomized rabbits into two groups; receiving intrapleural injections of either silver nitrate or talc slurry, and results showed silver nitrate is more effective than talc slurry pleurodesis [27]. Of note, each group had 70 rabbits and three subjects (4.3%) developed hemothorax in the silver nitrate group, whereas no animals in the talc group developed this complication [27]. Aside from this, there are also several studies reporting that silver nitrate pleurodesis leads to systemic inflammatory reactions, and causes pigment accumulation in the lung tissue [28, 29].

#### **d. Iodo povidone pleurodesis**

Iodo povidone, a topical antiseptic, appears an effective pleurodesis agent due to its low cost and wide availability. Although iodo povidone is an effective pleurodesis agent, several studies mentioned its tolerable side effects. Neto *et al.*; performed 61 iodo povidone pleurodesis in 54 patients, adverse effects occurred after 11 (18.0%) pleurodesis procedures [30]. The most frequent complication was mild thoracic pain that occurred immediately after ten (16.4%) procedures, and one patient (1.6%) developed pleural empyema [30]. In another recent study, again Neto *et al.*; researched the safety profile of iodo povidone

pleurodesis in malignant pleural effusion patients and reported the observed side effects of 60 patients [31]. The most frequent event was blood pressure alterations; 41 patients (68.3%) developed hypertensive peaks, whereas 4 patients (6.7%) developed hypotension [31]. Pleuritic pain was the second most frequent serious adverse event related to iodo povidone pleurodesis, and occurred in 33 patients (55.0%), and was mostly accompanied by serious hypertension and tachycardia [31]. The other side effects were followed as hypoxia, pleural infection, kidney injury, anemia, and nausea [31].

Jablonski *et al.*; published outcomes of iodo povidone pleurodesis in the management of prolonged air leaks and reported that tachycardia was the most common complication followed by dyspnea, and the patients in the iodo povidone pleurodesis group perceived the highest level of pain [32]. In some other studies, it was demonstrated that chest pain is the most frequently observed complication. Mahmudlou *et al.*; performed iodo povidone pleurodesis in 29 spontaneous pneumothorax cases and reported five (17.2%) patients suffered from chest pain [33]. Similarly, according to a meta-analyses published by Agarwal *et al.*; the only significant complication was varying degree of chest pain, after iodo povidone pleurodesis [34]. In general, no mortality was reported after iodo povidone pleurodesis, and it is considered as a manageable practice in terms of complications with low application costs, high efficiency, and fewer side effects with slight clinical symptoms.

#### **e. Tetracycline pleurodesis**

Tetracycline is an antibiotic which can be used to achieve pleurodesis. With the decrease of the production of the liquid form of tetracycline in years, the frequency of its use in pleurodesis has also declined. Although it is reported that generally it is a safe application, some side effects may also be observed. Chaugle *et al.*; published a case report and described chemical burns of pleura after overdose tetracycline pleurodesis [35]. It has been reported that tetracycline pleurodesis was applied in the form of “continuous intrapleural infusion” for three days, and the pleurodesis was not successful, and the necrotic scar areas were observed in the pleura [35]. Smythe *et al.*; reported an acute renal failure complication of tetracycline pleurodesis, and concluded intrapleural tetracycline administration might lead to increase serum drug levels and systemic drug side effects might therefore be noted [36]. In another case report, Abraham *et al.*; reported a pyopneumothorax with bronchopleural fistula complication after tetracycline pleurodesis [37]. In a

prospective randomized clinical trial, Tabatabaei *et al.*; reported a comparative study of tetracycline versus silver nitrate pleurodesis; all patients in the tetracycline group had side effects [38]. In the tetracycline pleurodesis group, all of the patients had fever and chest pain, whereas, in the silver nitrate pleurodesis group, fever was detected in 12%, chest pain was suffered in 48% of cases [38]. In another comparative study published by Keeratchananont *et al.*; tetracycline pleurodesis versus autologous blood pleurodesis were compared; fever and chest pain complications was reported as significantly higher in the tetracycline pleurodesis group [39]. In general, tetracycline pleurodesis is a pleurodesis method with decreasing frequency of use and with low side effect possibility, but also it has been reported to have serious side effects.

#### **f. Autologous blood pleurodesis**

Among the pleurodesis methods mentioned here, probably the least side effects, low costs, and with highest cost/benefit rates are the autologous blood pleurodesis (ABP) and dextrose pleurodesis. There are few complication reports for ABP. The serious complication after ABP is empyema which affected three of 32 patients (9.4%) in a clinical study [40]. Fever, pleural effusion, and pneumothorax were reported as minor complications after ABP [40, 41].

One of the difficulties in applying ABP is the clotting of the blood within a few minutes after taken from the vessel until the application of it from the chest tube. For this reason, the blood taken from the patient must be applied with the chest tube as soon as possible without clotting. Wide-caliber drains must be preferred for the application; because in drains with small diameters, fast clotting will occur when the blood is passing through catheter, and this will decrease the efficiency of the process.

#### **g. Hypertonic Dextrose Solution pleurodesis**

The most commonly preferred solution is 50% dextrose solution and this procedure documented as safe, cost-effective, easy to administer, and has low complication rates [42-44]. A temporary elevation of the blood sugar level after dextrose pleurodesis and chest pain were the only adverse effects [42].

#### **h. Pleurodesis with cytotoxic agents**

Several different agents such as cisplatin, quinacrine, thiotepa, doxorubicin, nitrogen mustard, 5-fluorouracil, OK-432, and mitoxantrone have been used in the attempts to control pleural effusions by cytotoxicity rather than sclerosis. Most of these drugs are known as chemotherapeutics and plays a major role

in the treatment of several cancers. The penetration depth of cytotoxic drugs after intrapleural administration was appears to be five millimeter or less [45].

Cisplatin is the drug that has been the most widely used for intracavitary chemotherapy, and that the local pharmacologic advantage achieved by intrapleural administration can lead to tumor regression [46]. Intrapleural cisplatin carries the potential of significant toxicity such as renal toxicity, and emesis; because a significant amount is absorbed systemically [47]. Nitrogen mustard controlled the effusions in approximately one third of the patients but caused significant adverse effects such as chest pain, fever, and associated with bone marrow depression [45]. Thiotepa and 5-fluorouracil had fewer side effects but were no better at controlling malignant pleural effusions [45]. Intrapleural doxorubicin administration was associated with pleuritic pain, fever, nausea, and vomiting [45]. Quinacrine was an effective sclerosant that controlled effusions up to 80% of patients but caused severe pleuritic pain, fever, hypotension, hallucinations, and seizures [45]. However, Janzing *et al.*; reported the effectiveness and safety of quinacrine pleurodesis for the patients of recurrent pneumothorax and persistent air leaks [48]. Sreter *et al.*; performed pleurodesis with mitoxantrone for malignant pleural effusion and reported the safety of the procedure as 80.9% [49]. However, four of 21 patients (19.1%) developed side effects, the leading side effect was fever (n=3, 14.3%), followed by diarrhea (n=1, 4.8%) [49].

Immunomodulating agents such as *Corynebacterium parvum* and OK-432 are more expensive and difficult to obtain rather than antibiotics, talcum powder, and other agents. Most of these agents were abandoned, either because of their ineffectiveness or because of significant toxicity or expensiveness.

#### **2. Pleurodesis with various agricultural substances, proteins or products:**

Some of the above mentioned, conventionally used, pleurodesis agents have high cost-profile, most of them have several side effects, some of these agents are being not easily found, and some of them are not used in some countries. Therefore, these reasons make it inevitable to develop new and more efficient agents. In addition, new products are also necessary to complete the pleurodesis process with success without any side effects or with slight side effects.

Researchers have shown that several agricultural substances, proteins or products may be used for pleurodesis by making use of various

properties of them. These endeavors of pleurodesis could be named as “phyto therapeutic pleurodesis”; and literature revealed that this enthusiasm intensify mostly on viscum album (mistletoe). Beside viscum album, phyto therapeutic pleurodesis was also performed with some components obtained from *copaifera multijuga* and *brucea javanica* plants. Sericin, on the other hand, is a protein component of silkworm cocoons, and has been evaluated in this group since it is an agriculture-originated product. As a last item, olive oil has also been evaluated in this category since it is of plant origin.

#### a. Viscum album pleurodesis

Viscum album, commonly known as mistletoe, is a semi-parasitic shrub which grows on other trees and has a long history of use in the folk medicine. It has been shown in various studies that it may be used as a chemical pleurodesis agent aside from its diuretic, antispasmodic, and properties that aid digestion [50-53]. Among the phyto therapeutic pleurodesis agents, it was applied for the first time and it is the most frequently investigated agent. Additionally, its side effects have been revealed in a better manner, and it is the richest agent in terms of literature data. In most of the data on clinical applications, it is observed that viscum album is used in the treatment of malign pleural effusions; whereas, its use in prolonged air leak, pneumothorax, and chylothorax is limited.

Performing pleurodesis with viscum album extract has been studied in several laboratory and clinical researches in the literature. Ahn *et al.*; designed a rat study and they used viscum album extract for chemical pleurodesis [50]. They compared talcum powder pleurodesis with mistletoe extraction and reported there was no significant difference in the grade of pleural adhesions between two groups [50]. These researchers suggested that pleurodesis using viscum album extraction has comparable effect to pleurodesis using talcum powder [50].

Gaafar *et al.*; compared viscum album pleurodesis with bleomycin pleurodesis in malignant pleural effusion patients; the overall clinical response was detected as successful in 61.5% of the viscum album group, and only 30% of the bleomycin group [51]. The side effects in the viscum album group included fever, chills, headache, and allergic reactions which were controlled by ceasing of the procedure and steroid injection [51]. In contrast, Elkasas *et al.*; performed a similar comparative study, pleurodesis with viscum album versus bleomycin in the malignant pleural effusion patients, and they reported bleomycin

pleurodesis had a better clinical response [54]. In the bleomycin pleurodesis group, complete remission rate was calculated as 72%, while in the viscum album pleurodesis group it was 52% [54]. There were higher success rate among the bleomycin group with statistically significant difference [54]. Moreover, hospital stay was shorter in the bleomycin group [54]. According to Elkasas *et al.*; bleomycin pleurodesis has some advantages over viscum album pleurodesis due to lower incidence of failure, being more economic, and for the shorter hospital stays [54]. Fever and pleuritic pain were the only side effects in the both groups; two patients (8%) had fever, and two patients (8%) suffered from pleuritic pain in the bleomycin group, whereas only one (4%) patient had fever in the viscum album group [54].

In another clinical study, Cho *et al.*; performed chemical pleurodesis using viscum album extraction in 62 malignant pleural effusion patients [52]. Of the patients, 49 (79.0%) had complete response, 11 (17.7%) had partial response, and two (3.3%) had no response [52]. There were two serious adverse effects, a pleural inflammation and pain, but all were recovered without sequel [52]. El-Kolaly *et al.*; also studied the pleurodesis with viscum album, and compared it with iodo povidone and vincristine pleurodesis in malignant pleural effusion cases [53]. According to El-Kolaly *et al.*; failed pleurodesis was higher in the vincristine group; successful pleurodesis was highest in the viscum album and iodo povidone groups (both groups had a success rate of 73.3%) [53]. However, in the viscum album pleurodesis group (n=15), pleuritic pain (n=8, 53.3%), and fever (n=6, 40%) were the side effects; these ratios were higher than iodo povidone pleurodesis group [53]. Therefore, El-Kolaly *et al.*; concluded that iodo povidone pleurodesis is an ideal sclerosant agent due to its high efficacy, availability, cheapness, and had lower side effects, but the overall effectiveness of viscum album pleurodesis was better than vincristine pleurodesis [53]. El-Feky *et al.*; performed a similar study and compared viscum album pleurodesis with vincristine pleurodesis [55]. The success rate of pleurodesis was significantly higher in the viscum album group (70%) than in the vincristine group (63.3%), while side effects were not significantly different between both groups [55]. According to El-Feky *et al.*; the side effects of viscum album pleurodesis group (n=60) were as follow; pleuritic pain (n=11, 18.3%), fever (n=9, 15%), loculated pleural effusion (n=8, 13.3%), and empyema (n=1, 1.7%) [55].

Beside these complications, there were some case reports in which acute pneumonitis and ARDS complications depending on viscum album pleurodesis

were published. Cho *et al.*; reported an acute pneumonitis after repeated administration of viscum album pleurodesis, in a persistent air leakage patient after lingular segmentectomy [56]. The patient recovered with supportive treatment modalities without any clinical sign [56]. In another case report, Noh *et al.*; published an ARDS after viscum album pleurodesis [57]. In the report, a primary spontaneous pneumothorax patient underwent video-assisted thoracoscopic surgery, after multiple wedge resections viscum album extract was administered into the pleural space [57]. On the third post-operative day, the patient started to complain of worsening dyspnea, and chest x-ray revealed bilateral infiltrates. Patient was intubated and supportive treatment modalities including steroids was established [57]. After three days of steroid administration, x-ray infiltration was resolved and patient was weaned from mechanical ventilation [57]. In the above mentioned presentations, it is understood that viscum album pleurodesis is used with the highest frequency in malignant pleural effusions, followed by extended air leak and spontaneous pneumothorax cases. Beside these clinical application fields, Cho *et al.*; reported the chemical pleurodesis of viscum album in infants with congenital chylothorax [58].

#### **b. Copaifera multijuga pleurodesis**

Copaiba oils are produced by exudation from the trunks of trees, belonging to the genus *Copaifera* [59]. The effects attributed to copaiba oils in the folk medicine include anti-inflammatory, antimicrobial, antitumor, and urinary antiseptic activities [59-62]. It also used externally as a wound-healing agent and has neuroproductive activities [60, 63].

Da Silva *et al.*; researched the effectiveness of copaiba oil in the treatment of acne vulgaris and reported that there was a significant decrease in the surface affected with acne in the areas treated with 1.0% copaiba essential oil preparation [64]. Martini *et al.*; researched the usefulness of copaifera multijuga oil-resin in the cutaneous wound healing process in rats [63]. They found that copaiba oil was more capable of converting type III (young) collagen to type I (mature) collagen, a fact that has a positive effect, since the higher amount of mature collagen, the greater the wound's mechanical resistance [63]. Gomes *et al.*; designed an animal study and reported that copaifera multijuga oil showed antineoplastic properties against Erlich ascetic tumor and other solid tumors, during ten days treatment by oral gavages in rats [61]. The anti-inflammatory effect of copaifera multijuga oil has also been demonstrated. Kobayashi *et al.*; performed a rat study to analyze anti-inflammatory effects of copaifera

multijuga oil [62]. The results obtained from the study suggested that copaifera multijuga oil exhibited an anti-inflammatory effect in the induced pleurisy model *in vivo* and chemotaxis *in vitro*, demonstrated by reduced leukocyte migration to the rats' pleural cavity [62].

In the literature, the pleurodesis effectiveness of copaifera multijuga oil has been demonstrated by a study. Westphal *et al.*; performed a rat study in order to compare silver nitrate pleurodesis with copaiba oil pleurodesis [65]. The mean values of macroscopic alterations grade and acute inflammatory reaction grade was higher in the copaiba oil pleurodesis group than in the silver nitrate pleurodesis group at the first 24 hour [65]. Fibrosis and neo-vascularization mean values in the visceral pleura were also higher in the copaiba oil pleurodesis group rather than in the silver nitrate pleurodesis group at 504<sup>th</sup> hour [65]. However, the grade of the alveolar edema was higher in the silver nitrate pleurodesis group, this alteration was not observed in the copaiba oil pleurodesis group [65]. Finally, the presence of bronchopneumonia was significant in four animals in the silver nitrate group even in the early period, this complication was observed in the copaiba oil group in two subjects at 48<sup>th</sup> and 504<sup>th</sup> hours [65]. Therefore, researchers concluded that both groups promoted pleurodesis, better results obtained from copaiba group; however, silver nitrate group presented greater aggression to the pulmonary parenchyma [65].

#### **c. Sericin pleurodesis**

The cocoon shell of silkworms, *Bombyx mori*, is composed of two natural macromolecular proteins called fibroin and sericin [2, 66]. Fibroin accounts 75% of all silk protein and fundamental macromolecular protein used in textile industry. However, sericin is a by-product of textile industry, widely known as natural gum-like protein, and the removal of sericin from silk fibroin is accomplished by a specialized process called "degumming" [67]. Sericin has a widely application field in cosmetics sector as an antiwrinkle and antiaging agent; in addition, it can be used as an antioxidant or food additive in the food industry [68]. The cream form of sericin has been showed to reduce uremic pruritus in hemodialysis patients [69]. Favorable effects of sericin on wound healing has also been demonstrated in several studies, such as decreased inflammatory reaction, the reduction in wound size, and increase in epidermal thickness and vascularization [70,71,72]. Moreover, sericin is an additive in the cell culture media due to its cell protective activity; it has an effect to increase growth and proliferation of cells [73, 74]. Sericin also

has hypocholesterolemic effect in high-cholesterol fed rats [75].

In the review of literature, intrapleural administration of sericin was only performed by Yazicioglu *et al.*; in a rat study [2, 66]. The intrathoracic administration of sericin results in an increase in fibroblastic activity and fibrosis in the visceral pleura without any significant adverse effect on lung parenchyma [2]. Additionally, there were no foreign body reactions and no evidence of biological glue on the specimens in the sericin pleurodesis group, and the rats in the sericin pleurodesis group had lower inflammatory reactions compared with control group [2]. Moreover, intrapleural sericin administration increases plasma native thiol and total thiol levels which assists antioxidative activity and prevent free radical induced damage [66]. Significantly higher native thiol levels and the higher total thiol levels in the sericin group support the hypothesis that sericin application may increase antioxidative features, may establish a quick regeneration in the lung tissue, and may prevent carcinogenesis [66]. According to Kaewkorn *et al.*; sericin reduces colon cancer cell viability by inducing cell apoptosis via caspase-3 activation and down regulation of Bcl-2 expression [76].

It is logical to use a protein, which is already a natural adhesive, in gluing pleural surfaces to each other. However, it has not been yet cleared that which mechanism of sericin application cause fibrosis, and how sericin demonstrate its antioxidative effect. Studies on sericin increase with each passing year, and there is a need for comparative studies. Clinical studies are also necessary both for sericin and copaiifera multijuga pleurodesis methods.

#### **d. Brucea javanica**

*Brucea javanica* was first mentioned in the Chinese medical monograph published in the sixteenth century [77]. In Chinese medicine, *brucea javanica* is characterized as an antipyretic and detoxifying plant, and widely used in the treatment of several cancers including lung cancer [77-79]. Not only in the cancer treatment, but also it has potent anti-inflammatory effect with low toxicity [77]. *Brucea javanica* contains quassinoid compounds called bruceolides that have anticancer and antiparasitic properties [77]. *Brucea antidysenterica*, as its name suggests another plant from the same family and have been used in the traditional treatment of malaria falciparum for years [80]. Kefe *et al.*; designed an animal study and reported that the crude aqueous, methanol, and chloroform extracts of *brucea antidysenterica* plant possesses significant

antimalarial effects, inhibits parasitaemia in a dose-dependent manner, and prevents body weight loss [80].

The anticancer activity of *brucea javanica* oil emulsion has been studied in a few reports. Nie *et al.*; reported the effect of *brucea javanica* oil emulsion, in addition with chemotherapy and radiotherapy for lung cancer [79]. They concluded that injection of *brucea javanica* oil emulsion plus chemotherapy and radiotherapy may have positive effects on lung cancer patients in response rate, improvement of quality of life, and reducing some adverse effects compared with chemotherapy and radiotherapy alone [79]. Similarly Wang *et al.*; reported *brucea javanica* oil emulsion combined with cisplatin treatment for malignant pleural effusion of lung cancer [78]. They performed treatment from chest tube, just as being performed in the pleurodesis; the short-term effects and quality of life in the combined group (*brucea javanica* oil emulsion pleurodesis accompanied with cisplatin) were significantly superior to chemotherapy alone treatment group [78]. The data on the use of *brucea javanica* oil are limited with cancer cases, and there are no literature data on the use of it in pneumothorax and in other pleural pathologies. The use of it in cancer cases is mostly in the form of cytotoxic agent.

#### **e. Olive oil pleurodesis**

The oldest application in the literature on using agricultural products for the purpose of pleurodesis is the olive oil application, and there is only one study on it, in the literature. Ofoegbu *et al.*; performed olive oil pleurodesis in five patients with poor respiratory reserve [81]. They advocated that when olive oil is in contact with the pleural surface, it elicits a slow but progressive inflammatory response, and this aseptic pleural inflammation causes adhesion or synechia between the visceral and parietal pleura [81]. In the same article they also mentioned that they performed a rabbit study in order to understand the histological changes during olive oil pleurodesis. The necropsy of rabbit lungs were revealed the proliferation of the pleural mesothelial cells with some fibrous reaction leading to overall thickening of the pleural surfaces [81]. There were some foreign body reactions, giant cells were particularly observed at the visceral layer [81].

The literature summary of the phyto therapeutic pleurodesis agents; the presence of laboratory and/or clinical studies, the area of usage in clinical applications, the presence of comparison studies, and the reported side effects are given in Table-1.

Table-1: A literature summary of phyto therapeutic pleurodesis agents.

	Laboratory study	Clinical study	Clinical application	Comparative study	Observed side effects
<b>Viscum album</b>	Yes (Rat study)	Yes	Malignant pleural effusions Persistent air leaks Pneumothorax Chylothorax	Viscum album vs. Talcum powder Viscum album vs. Bleomycin Viscum album vs. Iodo povidone Viscum album vs. Vincristine	Fever, Pleuritic pain, Headache, Empyema, Loculated effusions, Chills, Allergic reaction, Acute pneumonitis, ARDS
<b>Copaifera multijuga</b>	Yes (Rat study)	None	Not mentioned	Copaifera multijuga vs. Silver nitrate	Bronchopneumonia
<b>Sericin</b>	Yes (Rat study)	None	Not mentioned	None	Not mentioned
<b>Brucea javanica</b>	None	Yes	Malignant pleural effusions	None	Not mentioned
<b>Olive oil</b>	Yes (Rabbit study)	Yes	Spontaneous pneumothorax	None	Not mentioned

## CONCLUSIONS

The most frequently used pleurodesis agent is the talcum powder, followed by doxycycline, silver nitrate, iodo povidone, and other applications. However, the published reports revealed all the pleurodesis agents have various systemic and/or local side effects. Serious side effects such as respiratory difficulty that requires mechanical ventilation, ARDS, mortality may be observed as well as some mild side effects like fever, chest pain, asymptomatic respiratory difficulty, and asymptomatic cardiac problems. In addition, the cost profiles of the majority of these methods are high for developing or underdeveloped countries. Moreover, some pleurodesis substances may not be available in some countries or may not be found easily. For these reasons, there is a need for new pleurodesis agents with high efficiency, low side effect potential, low cost profile, high cost-effectiveness, easy to produce and obtain. Also this agent should be used widely all over the world, and have an easy application to patients. For these purposes, it has been observed that researchers have tried to use various agricultural substances, proteins or products for the purpose of pleurodesis, and designed several laboratory or clinical studies to reveal the efficiency of these substances.

It has been observed that the studies on viscum album pleurodesis are mostly from Egypt and South Korea; all of the studies on copaifera multijuga are from Brazil, the only study on sericin pleurodesis is from Turkey, the studies on brucea javanica are from Peoples' Republic of China, and the only study on olive

oil pleurodesis is from Nigeria. Researchers from different countries have agreed on a consensus, and this consensus is on using natural products and trying to use new substances for pleurodesis with low costs, high efficiency, and with low side effect potential.

It has also been observed that the comparative studies of phyto therapeutic pleurodesis agents versus conventional pleurodesis agents are extremely few in number; the literature on this topic is being formed newly. When the literature is reviewed, only viscum album pleurodesis has clinical application studies and comparative studies. Both copaifera multijuga and sericin pleurodesis has been studied in a single animal study for each agent. There is only one study in which copaifera multijuga is compared with silver nitrate; however, sericin has not been compared with any other agents. In order to spread the use of these agents for pleurodesis, this lack in the literature has to be filled. In addition, the issue of with which mechanisms phyto therapeutic pleurodesis agents ensures the efficiency of pleurodesis is another area that awaits clarification.

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