

## ***Rabdosia rubescens* and esophageal cancer- An overview**

<sup>1</sup>Sankaradoss Nirmala, <sup>1</sup>R. Balambigai, <sup>1</sup>R. Harishree, <sup>1</sup>K.M. Hema Rohini,  
<sup>2</sup>S. Dhanalakshmi, <sup>1</sup>M. Sivakumar and <sup>\*</sup>P. Nandanasabapathi

<sup>1</sup>Faculty of Pharmacy, Sree Balaji Medical college campus, Bharath Institute of Higher Education and Research, Chromepet, Chennai-600044 (India)

<sup>2</sup>GRT Institute of Pharmaceutical Sciences and Research, Thirutani.

Corresponding Author: S.Nirmala [nirmala.cognosy@gmail.com](mailto:nirmala.cognosy@gmail.com)

M. 9505421144

<sup>\*</sup>Formulation R&D Sunglow Life Science Pvt. Ltd. Chennai-600100 (India)

### **Abstract**

*Rabdosia rubescens* (Lamiaceae) is an herb. The whole plant is used to make medicine. It has been widely used for decades to treat sore throats, tonsillitis, colds and headaches, bronchitis, chronic hepatitis, joint rheumatism, snake and insect bites, and various cancers. *Rabdoisa rubescens* contains many active ingredients such as terpenoids, flavonoids, polysaccharides and organic acids. According to recent studies, *Rabdosia rubescens* has the ability to eliminate heat, detoxicate, fight cancer and bacteria, increase blood flow to treat pain, and clear tumours.

**Key words :** *Rabdosia rubescens*, esophageal cancer, Lymph node, Adenocarcinoma, GERD.

**I**n terms of prognosis and mortality rate, esophageal cancer is a serious malignancy. Globally, more than 4 lakhs people died from this disease in 2005<sup>21</sup>. In developing nations, over 80% of cancer cases and deaths are caused by esophageal carcinoma, which is the eighth most common cancer and the sixth leading cause of cancer related death<sup>5</sup>. It is estimated that over four lakhs ninety thousand new cases of esophageal cancer occurred in 2005. By 2025, esophageal cancer prevalence is expected to increase by 140% despite other types of cancer declining in incidence over the next few years<sup>21</sup>. Esophageal cancer is most

prevalent in two geographical regions, one from North Central China through central Asia to northern Iran and other from eastern to southern Africa. Chinese citizens are more than half the number of people who die of esophageal cancer. There is a male-dominant trend in esophageal cancer. It is estimated that two to three times more males than females suffer from ESCC worldwide. In general, the EAC histological subgroup has an even stronger male predominance<sup>18</sup>. Squamous cell carcinoma (SCC) and adenocarcinoma (AC) are the two main kinds of EC, respectively, based on cell shape<sup>7</sup>. Dietary choices and

hereditary factors are the main causes of EC. Dietary factors are a major contributor to the development of EC; epidemiological studies have shown that foods high in vitamins and phytochemicals frequently have anti-carcinogenic qualities<sup>28</sup>. Herbs used as medicines have long been used in traditional illnesses. *Rabdosia rubescens*, for example in the case, has widely been utilised in EC therapy<sup>8,11</sup>. Gastroenteritis and diarrhoea have traditionally been treated with *Coptidis rhizome*<sup>16</sup>. According to report medicinal herbs offer a distinct advantage in EC therapy by preventing the development of cancer cells, slowing the spread of the disease, boosting immunity, reducing cancer relapses and metastasis, raising the 5-year survival rate, and much more<sup>2,3</sup>. Additionally, when paired with radiotherapy and chemotherapy, medicinal herbs with minimal side effects or toxicities may enhance the therapeutic impact<sup>2</sup>.

#### *Etiology :*

About 90% of esophageal squamous cell carcinoma cases in the US are caused by a history of smoking, alcohol usage, and a diet poor in fruits and vegetables. Risk factors for this type of cancer in poorer nations are less well known but this may include poor nutrition, a low consumption of fruits and vegetables, and drinking hot beverages. Squamous cell tumour of the upper oesophagus have been linked to an increased occurrence of human papillomavirus (HPV) infection. Esophageal squamous cell carcinoma is more likely in people who already have pre-existing anatomical conditions like achalasia, caustic strictures, gastritis. The chance of acquiring cancer by age 70 ranges from 40% to 90% for those with tylosis, a rare autosomal dominant disease

linked to non-epidermolytic palmoplantar keratosis (also known as Howel-Evans Syndrome). Squamous cell carcinoma is more likely to develop in people who have Fanconi anaemia, an autosomal recessive condition that also raises the possibility of hematologic malignancies, pancytopenia, and congenital abnormalities. Oral bisphosphonates have been related to squamous cell carcinoma and adenocarcinoma of the oesophagus in post-marketing monitoring studies.

In the United States, gastroesophageal reflux disease (GERD), a high body mass index, a background of smoking, and a diet poor in fruits and vegetables are associated with Barrett's metaplasia, which accounts for 80% of cases. Proton-pump inhibitors, NSAIDs, fruits, vegetables, folate, vitamin, and a high-cereal diet can all help prevent the onset and improvement of Barrett's oesophagus and, consequently, esophageal adenocarcinoma. However, despite these associations, no one of these factors has been proven to be a preventive measure.<sup>4,29</sup>

#### *Epidemiology:*

Esophageal cancer is the sixth most prevalent cancer worldwide and the fifth most common cancer in the United States, with an estimated 16940 cases per year. The "esophageal cancer belt" is the area where esophageal cancer risk is highest and includes areas like Northern Iran, Southern Russia, Central Asian Nations, and Northern China, where 90% of incidents of squamous cell cancer are found. In contrast, the United States is regarded as a low-risk region, with esophageal adenocarcinoma incidence rising mostly due to a rise in obesity and GERD, and squamous cell

carcinoma steadily decreasing due to a long-term decline in tobacco and alcohol usage. White men with adenocarcinoma are primarily affected by the disease. On the other hand, Asians and Blacks have the greatest incidence rates of esophageal squamous cell carcinoma.<sup>20</sup>

*Pathophysiology:*

Little polypoid excrescences, denuded epithelium, and plaques, which are typically found in the middle of the oesophagus, are the precursors of esophageal squamous cell carcinoma. To aid in the diagnosis of the early lesion, normal squamous epithelium containing glycogen should be distinguished from malignant squamous cells deficient in glycogen by tissue staining with Lugol's iodine. Advance lesions are cephalad extending. Circumferential ulcerated lesions that invade the submucosa. Transmission happens through the lymphatic system to local lymph nodes, but in a third of individuals, the disease will spread to distant sites such the liver, lungs, and bones as well as invade the bone marrow.<sup>1,15</sup>

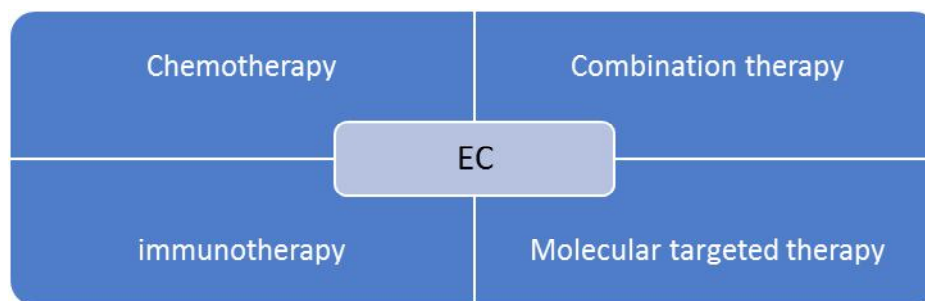
Patients with Barrett's oesophagus typically undergo surveillance using upper

endoscopy and biopsy to look for signs of dysplasia in the tissue. Those without dysplasia have an incidence rate of 1.0 cases per 1000 person-years for cancer, whereas, patients whose index endoscopy revealed low-grade dysplasia had an incidence rate of 5.1 cases per 1000 person-years for adenocarcinoma. Esophageal adenocarcinoma had an annual risk of 0.12% (95% CI, 0.09, 0.15).

Aggressive treatment for high-grade dysplasia is recommended, including the potential of surgical excision: Early metastases develop in close by or nearby lymph nodes. Tumor markers (TP53), for example, can serve as predictors of possible malignant disease progression.

Evaluation of the HER2 gene and protein has been linked to lymph node metastasis and tumour invasion, both of which are associated with decreased survival. Adenocarcinoma (30%) and squamous cell carcinoma (13%), however, overexpress HER2. For all metastatic adenocarcinomas, HER2s advised; this is initially confirmed using the immunohistochemistry score (negative for 0 or 1+ and positive for 3+, with reflex FISH for 2+)<sup>1,15</sup>.

**Available treatment of EC:**



*Chemotherapy :*

Chemotherapy has the benefits of slowing tumour growth and limiting distant metastasis, making it the primary treatment for EC. The most extensively used chemotherapeutic agents for EC are doxorubicin (Dox), 5-fluorouracil, and cisplatin (DDP).<sup>23</sup>

*Combination therapy :*

The widely used combination therapy drugs are  $\beta$ -Carotene and 5-FU, 5-FU and cisplatin, CA3 and 5-FU, VE-822 and cisplatin, Hesperetin and 5-FU, Puerarin and 5-FU, ABT-263 and 5-FU, Tiplaxtinin and cisplatin.<sup>23</sup>

*Immunotherapy :*

Typically, antigen-presenting cells, in especially dendritic cells, are able to detect and phagocytize antigen-induced inflammation on the surface of tumour cells, then transmit the resultant antigens to T or B lymphocytes to trigger an adaptive response. To circumvent immune response, tumour cells have created a number of different ways<sup>27</sup>. ICIs and tumour vaccines are now the two main immunotherapy approaches for EC.

*Molecular targeted therapy :*

EGFR, HER2, and VEGF are the three major targets of molecular targeted therapy for EC.<sup>23</sup>

*Available herbal drugs for EC:*

- *Rabdosia rubescens* (8,11)
- *Coptidis rhizoma* (8,11)
- Ma De (16)

*Rabdosia rubescens :***Scientific classification**

**Kingdom:** Plantae

**Phylum:** Tracheophyta

**Class:** Magnoliopsida

**Subclass:** Magnoliids

**Order:** Lamiales

**Family:** Lamiaceae

**Genus:** *Isodon* (Schrad. ex Benth.) Spach

**Species:** *Isodon rubescens* (Hemsl.) H. Hara

**Synonym:** *Rabdosia rubescens* (Hemsl.) H. Hara (9)

*Rabdosia rubescens* is a kind of medicinal plant, tastes bitter and sweet, it is cold in nature. Belong to three channel tropisms for the liver, lungs and stomach, it eliminates heat, prevents infection, promotes blood circulation and stops cancer. This herb, originally from an herb used to relieve famines in Henan province, is one of the most famous medicinal herbs in the province. There is evidence for the effectiveness of *Rabdosia rubescens* in the treatment of esophageal cancer. *Rabdosia rubescens* had been found by the esophageal cancer research center to have a unique anticancer effect, which then has become widely used in clinical practice as a powerful antibiotic.<sup>26</sup>

*Pharmacological Actions :*

There may be medical and financial advantages to using *Rabdosia rubescens* for this anti-cancer, antibacterial, anti-inflammatory, immunomodulatory, and antioxidant properties. The use of a single drug and its chemical components in treating *Rabdosia rubescens* has been the subject of numerous investigations in recent years, but there are only a small number of references to these treatments in Chinese formulas, Chinese patent medicines, and dietary therapy. There is a dearth of literature on the pharmacological effect of its equivalent chemical components, despite the

fact that there is no scarcity of literature on the pharmacological action of it. So that the drug in the field of illness prevention and treatment would receive greater attention, this article described the pharmacological effects of the relevant chemical composition, formula, and Chinese patent medicine application.

*The pharmacological effect of Terpenoids:*

The terpenoids in *Rabdosia rubescens* have the highest content biological activity, medicinal value, economic value. Dimethylin has been shown in prior research to have anti-inflammatory, mediated immunity, antioxidant and antibacterial actions<sup>19</sup>. By preventing the production of PGE2 and epoxygenase-2(cox-2), p-nf-kappa B expression, dimethylin has been shown to suppress colon cancer LoVo cell growth and trigger apoptosis<sup>25</sup>. The effects of *Rabdosia rubescens*, which prevent the mitosis of pc-3 and LNCaP prostate cancer cells and enhance the expression of the autophagy-associated protein map1-lcc, can induce cell autophagy<sup>12,14</sup>. *In-vitro*, the diterpenoids KY3 of *Rabdosia rubescens* a novel active component, can damage the microtubule structure of EC109 and prevents its proliferation<sup>13</sup>.

*The Pharmacological effects of flavonoids:*

They are a crucial component of Chinese herbal therapy and are extremely prevalent. According to reports, flavonoids have antibacterial, anti-inflammatory, dilated coronary arteries, and liver protecting properties<sup>24</sup>. The study found that *Rabdosia rubescens* total flavonoids can increase the activity of antioxidant enzymes, inhibit the

production of oxygen free radicals during exercise, and improve the ability of mice to exercise while lowering the risk and mortality of mice with cerebral ischemia reducing the area of cerebral infraction, and improving the protective effect of ischemic preconditioning on brain injury<sup>6</sup>.

*The pharmacological effects of polysaccharides:*

RPPSIIA has been reported to have strong immune biological activity in the four polysaccharides (RPPS) components. The literature reports that RPPSIIA has lipid and water-soluble components<sup>10</sup>. The polysaccharide of *Rabdosia rubescens* has a beneficial effect on removing diphenyl benzoyl hydrazine (DPPH) and hydroxyl radicals, thereby providing anti-oxidative activity<sup>22</sup>. In addition, dangling grass has an obvious effect on bladder tumors in C57BL/6 mice, and in the process of perfusion therapy the important organs in the mice were not affected significantly<sup>30</sup>.

*The pharmacological effects of organic acids :*

While reports of the antibacterial properties of the extract of *Rabdosia rubescens* have been made both domestically and internationally, its primary active ingredient is yet unknown. The main antibacterial properties of *Rabdosia rubescens* are ferulic acid and salicylic acid, according to recent literature. In comparison to salicylic acid and ferulic acid shown some antibacterial efficacy against staphylococcus aureus (SA) and methicillin-resistant *Staphylococcus aureus* (MRSA)<sup>17</sup>.

*Side effects :*

There is no significant or evident side effects in patients who were treated with *Rabdosia rubescens*. Only few patients experience symptoms like mild abdominal symptoms such as diarrhoea, gurgling sound and others and these symptoms go on their own without any sort of treatments. Few patients experienced itching of skin and there is no liver, renal, cardiac and bone toxicity in patients who took long time therapy.

*Rabdosia rubescens* has an effect of detoxicating, promoting blood circulation to arrest pain and antitumour, antibacterial, anticancer, and has been praised by experts as the king of Chinese medicine.

In the clinical health care is used for the treatment of precancerous lesions of gastric cancer, peptic ulcer, gastric reflux and lung cancer.

*Rabdosia rubescens* used for the early stages of esophageal cancer, controls and prolongs the survival time. When it is combined with chemotherapy *Rabdosia rubescens* could enhance the effect of chemotherapy on advanced esophageal cancer. No side effects found in patients treated with *Rabdosia rubescens*.

## References :

- An W., H. Lai, Y. Zhang, M. Liu, X. Lin, and S. Cao (2019) Apoptotic pathway as the therapeutic target for anticancer traditional Chinese medicines. *Frontiers in pharmacology*. 10: 758.
- Arts I.C., and P.C. Hollman (2005) *The American journal of clinical nutrition*. 81(1): 317S-25S.
- Available at <https://www.gbif.org/species/7307417>; published in *J. Jap. Bot.* (1972).
- Chen S., J. Gao, H.D. Halicka, X. Huang, F. Traganos, and Z. Darzynkiewicz (2005) *International journal of oncology*. 26(3): 579-88.
- Cheng S., F. He, L. Fu, and Y. Zhang (2021) *RSC advances* 11(31): 18974-83.
- Cheng Y.F., H.S. Chen, S.C. Wu, H.C. Chen, W.H. Hung, C.H. Lin, and B.Y. Wang (2018) *Cancer medicine*. 7(9): 4193-201.
- Fukutake M., S. Yokota, H. Kawamura, A. Iizuka, S. Amagaya, K. Fukuda, and Y. Komatsu (1998) *Biological and Pharmaceutical Bulletin*. 21(8): 814-7.
- He S., J. Xu, X. Liu, and Y. Zhen (2021) *Acta Pharmaceutica Sinica B*. 11(11): 3379-92.
- Herszenyi L., and Z. Tulassay (2010) Epidemiology of gastrointestinal and liver tumors. *Eur Rev Med Pharmacol Sci*. 14(4): 249-58.
- Hongo M., Y. Nagasaki, and T. Shoji (2009) *Journal of gastroenterology and hepatology*. 24(5): 729-35.
- Jemal A., F. Bray, M.M. Center, J. Ferlay, E. Ward, and D. Forman (2011) *CA: a cancer journal for clinicians*. 61(2): 69-90.
- Khan T., M. Ali, A. Khan, P. Nisar, S.A. Jan, S. Afridi, Z.K. Shinwari (2019) *Biomolecules*. 10(1): 47.
- Ku C.M., J.Y. Lin (2013) *Food chemistry*. 141(2): 1104-13.
- Kuipers E.J., and M.C. Spaander (2018). *Digestive Diseases and Sciences*. 63: 1997-2004.
- Lambert R., and P. Hainaut (2007) *Best*

- practice & research Clinical gastroenterology*. 21(6): 921-45.
16. Li X., J. Wang, Z. Ye, and J.C. Li (2012) *International journal of biological sciences*. 8(6): 901-12.
  17. Liu F., G.Y. Liu, J. Zhou, X.P. Che, and R.F. Han (2011) *Zhongcaoyao Zazhi*. 42(02): 241-3.
  18. Liu J.B., and J.Y. Yue (2014) *Journal of international medical research*. 42(4): 984-92.
  19. Pei Baohe. (2013) [J]. *Chinese Journal of veterinary medicine*, (07): 53-54+57.
  20. Peng M., B. Liu, and M. Mao Study on the application of Chinese patent drug and chinese formula of *Rabdosia rubescens*. In IOP Conference Series: Materials Science and Engineering 2018 (Vol. 301, No. 1, p. 012060). IOP Publishing.
  21. Rui M.A., and W.U. Sheng-ben (2013) *Chinese Journal of Pharmacovigilance*. 10 (5): 286.
  22. Schizas D., P. Kapsampelis, and K.S. Mylonas (2018) *Journal of Translational Internal Medicine*. 6(2): 70-3.
  23. Schlottmann F., D. Molena, and M.G. Patti (2018) *Updates in Surgery*. 70: 339-342.
  24. Tramontano A.C., R. Nipp, N.D. Mercaldo, C.Y. Kong, D. Schrag and C. Hur (2018) *Digestive diseases and sciences*. 63: 2880-8.
  25. Wang C., L. Jiang, S. Wang, H. Shi, J. Wang, R. Wang, Y. Li, Y. Dou, Y. Liu, G. Hou, and Y. Ke (2015) *PloS one*. 10(6): e0130284.
  26. Wei X., Z. Chen, X. Yang, and T. Wu (2009) *Cochrane Database of Systematic Reviews*. (4).
  27. Wu T., X. Yang, X. Zeng, G.D. Eslick (2009) Traditional Chinese medicinal herbs in the treatment of patients with esophageal cancer: a systematic review. *Gastroenterology Clinics of North America*. 38(1): 153-67.
  28. Ye L.H., W.J. Li, X.Q. Jiang, Y.L. Chen, S.X. Tao, W.L. Qian, and J.S. He (2012) *Advances in Integrative Anatomy and Evolutionary Biology*. 295(3): 417-422.
  29. Yuan Z., P. Ouyang, K. Gu, T. Rehman, T. Zhang, Z. Yin, H. Fu, J. Lin, C. He, G. Shu, and X. Liang (2019) *Pharmaceutical biology*. 57(1): 710-716.
  30. Zhao Q., J. Yu, and X. Meng (2019) *Cancer Medicine*. 8(10): 4519-26.