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Lignans with Anticancer Activity

Lignanların Antikanser Etkileri

Belma KONUKLUGİL*

SUMMARY

In recent years lignans have gained great importance because of their biological activities These are anticancer antiviral, cathartic and allergenic activities. The most important of these is their anticancer activity This review includes lignans which show this activity and established the relationship between some lignan structures and their activites.

Key words: Lignans, anticancer activity.

ÖZET

Lignanlar son yıllarda bazı biyolojik etkileri nedeni ile önem kazanmışlardır. Bu etkiler antikanser, antiviral, katartik ve allerjik etkilerdir. Bunlar içinde en önemlisi antikanser etkileridir. Bu derleme de bu etkiyi gösteren lignanlarla, bazı lignanların yapı etki ilişkileri anlatılmıştır.

Anahtar kelimeler: Lignanlar, antikanser aktivite.

INTRODUCTION

From earliest times, plants have been used for medicinal purposes and to treat diseases. Egyptian pictographs, Babylonian clay tablet ideographs and Sumerian tablets have all shown that plants were used in the preparation of remedies From about 3000 B.C. the Sumerians used plants like *Cassia* and *Thymus* to make laxatives, antiseptics and other medicinal products (1).

The Greeks also contributed to this tradition, particularly with the studies of Dioscorides, a physician who lived in the first century.

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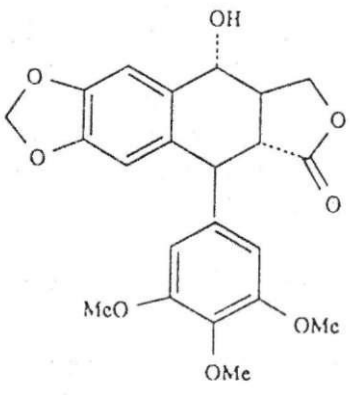
He wrote The Materia Medica, which lists over 600 plants that could be used for medicinal purposes, some of which are still important in modern medicine: These plants include *Aloe, Atropa, Colchicum, Hyoscyamus* and *Papaver.* Galen, a Greek pharmacist-physician, conducted similar researches and published about twenty books on the preparation of drugs (2). Other important contributors were the Chinese, whose Emperor Shen Nung wrote the "Pen Tsao Ching" around 2700 B.C. in which he described a hundred herbal remedies. Even today the Chinese still use many traditional medicinal techniques involving herbal remedies (2).

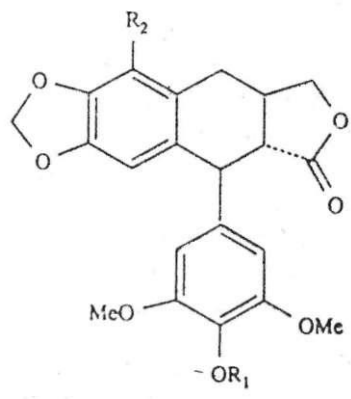
One very important area of research exploits the use of plants in the treatment of cancer. Cancer is the second most common cause of death after cardiovascular disease in Europe and USA. Therefore attempts are being made to isolate active constituents from natural sources that could be used to treat this very serious illness (3). Man has suffered from cancer for more than a million years. Evidence for this has been found by examination of an anthropoid unearthed in Java in 1891 (1).

Bone cancer was identified in some mummies in the pyramid of Gizeh. Ebers papyrus (1500 B.C.) also described symptoms of cancer and some primitive treatments. For example, for the treartment of abnormal hardening of a tissue or organ the external application of garlic *(Allium sativum).* Hippocrates, about 400 B.C. described many kinds of cancer and the application of some plant derived pastes for their cure. Garlic was also mentioned by him for the treatment of uterine tumours (1). Today, there is scientific evidence to show that garlic can be used against cancers of the skin, colon and stomach (5).

Two plant species which have a similar historical background are *Sanguinaria canadensis* and *Podophyllum peltatum.* These two plants were originally used by the North American Indians to treat cancer. Research on these plants has shown that some alkaloids isolated from *S. canadensis* have a significant effect on cancer cells (6). Chemical investigation of the resin of Podophyluml species has revealed the presence of several lignans, including podophyllotoxin, a-peltatin and 5-peltatin which show antitumour activity in mice (7). Further examples can. be found in. other plant species. Therefore it will be useful to study folkloric remedies when starting the chemical investigation of other plant species.



podophyllotoxin



$R_1 = H\ R_2 =$ α-peltatin

$R_1 = Mc\ R_2 =$ β-peltatin

Lignans are natural products which are formed by two C6-C3 units β–β′ linked. The term "lignan" was introduced by Harwoth to describe the dimers of phenylpropanoid (C6-C3) units linked by the central carbon atoms of their side chain. Lignans can be classifed in three groups;

1- non-oxygenated lignans.

2- oxygenated lignans

a) -butanolide
b) -monoepoxylignan
c) -bisepoxylignan

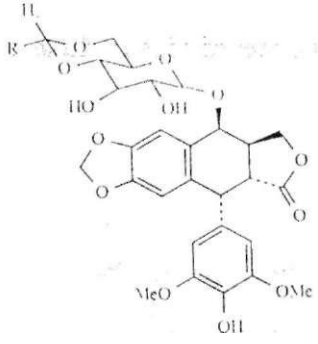
3- cyclolignans

a) -arynaphthalene
b) -aryltetralin
c) -dibenzocydooctadiene.

Lignans have been identified in some families many of which have been used in folk medicine. They have been isolated from all parts of plants (wood, bark, resin, roots, leaves, flowers, fruits and seeds) (7, 8).

There can be no doubt that the lignans have provided interesting examples of plant antitumour agents. Since 1942 the lignans have been of interest any numerous studies have been made on podophyllotoxin

groups of lignans from *P. peltatum* and *P. hexandrum* Two derivatives of podophyllotoxin are of clinical interest (VM-26) and (VP-213) and they have shown activity against Hodgkins' disease, reticulum cell carcoma and monocytic leukemia (9).



R=CH, etoposide (VP-16-213)

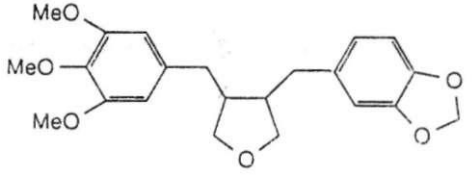
R = tenoposide (VM-26)

Antitumour activities of the other classes of lignans are also important. For example, burseran, a mono epoxylignan obtained from *Bursera microphylla* (Burseraceae) has also shown cytotoxic activity (10). A species, *Penstemon deustus,* which belongs to the Family Scrophulariaceae contains a furofuranoid lignan liriodendrin which can be used as a cytotoxic agent (11). Styraxin, another a furofuran lignan, isolated from *Styrax officinalis* (Styraxaceae), also has antitumour activity (12). In 1989 Trumm and Eich reported that the two benzylbutyrolactones, arctigenin and trachelogenin, showed strong cytotoxic activity. These two lignans have been isolated from *Ipomoea cairica* (Convolvulaceae) (13). Diphyllin is one of the arylnaphthalene derivatives which has cytostatic activity. This powerful action may be related to its close structural relationship with podophyllotoxin (14). Diphyllin. has been obtained from *Diphylleia grayi (15). D. cymosa* (Berberidaceae: Podophylloidea), *Justicia procumbens* (Acanthaceae) (16), *Cleistanthus collinus* (Euphorbiaceae) (17, 18). *Taiwania cryptomeriodides* (Cupressaceae) (19), and four Haplophyllum species (Rutaceae), H. *buxbaumi* (20). H. *tuberculatum* (14), *H. hispanicum* (21) and *H. cappadocicum* (22). 5-methoxypodophyllotoxin and podophyllotoxin have been isolated from *Linum album* (23).

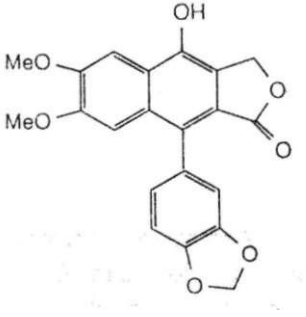
Two lignan lactones of the dibenzocyclooctadiene type, known as steganacin and steganagin, have significant cytotoxic activity both *in vivo* and *in vitro* These compounds have been obtained from an alcoholic extract of the South African tree *Steganotaenia araliaceae* (Umbelliferae) (24).

Anti-leukaemic action has been reported for wisktromol isolated from *Wikstroemia viridi- flora* (25).

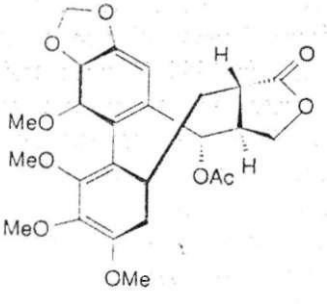
So far, 36 anticancer lignans have been identified and these are listed in Table 1.



burseran



diphyllin



(-) - Steganacin

Lignans With Anticancer Activity

Table 1. Lignans known to show anticancer activity

Compound name.

A) butanolide group lignan
arctigenin
(-)-trans-2-(3", 4", 5" - trimethoxybenzyl)-3(3', 4' methylenedioxybenzyl)
(-)-trans-2-(3", 4", 5" -dimethoxybenzlyV^O', 4' methylenedioxybenzyly) butyrolactone
trachelogenin
wikstromol

B) arylnaphthalene group lignan
diphyllin
diphyllinin
diphyllin acetate
diphyllin crononate
diphyllinin monoacetate
acethyl junapthoic acid
methyl junaphthoate
methyl acethyljunaphthoate
phyllanthostatin A

C) epoxylignan
(+)-dimethylisolariciresinol-2x-xyloside
burseran

D) bisepoxylignan
liriodendron

E) aryltetralin group lignan
desoxypodophyllotoxin
3'-demethylpodophyllotoxin
4'-demethylpodophyl!otoxin
5'-desmethoxypodophyllotoxin (morelsin)
4'-demethyldesoxypodophyllotoxin
5'-desmethoxy-B-peltatin-A-methylether
dehydroanhydropicropodophyllotoxin
podophyllotoxin
podophyllotoxin glucoside
picropodophyllotoxin
picropodophyllic acid
epipodophyllotoxin
justicidin A
justicidin B
nordihydroquqiaretic acid

E) dibenzocyclooctadiene lignan
stegnacin
stegnangin
stegnanol

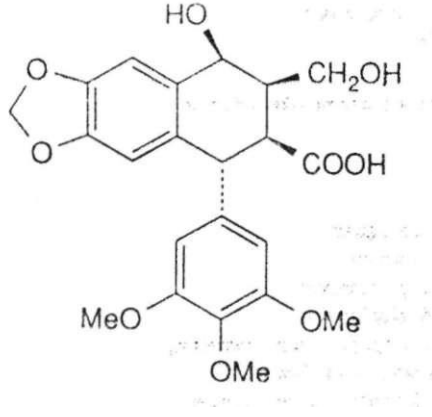
Belma -KONUKLUGİL

STRUCTURE-ACTIVITY RELATIONSHIPS PODPHYLLTOXIN AND RELATED COMPOUNDS

Lignans have great significance because of their anticancer activity. This is particularly true of the Podophyliotoxin group of lignans. There is no set structural trend which might explain some of the activity of lignans as anticancer agents. Many of the active forms do show the following features.

1. 5-membered lactone rings.
2. a 3, 4, 5-trimethoxyphenyl group
3. a methylenedioxy group.

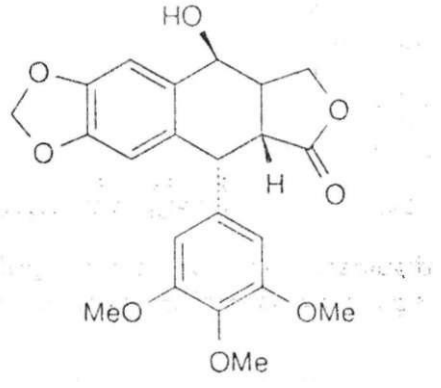
The presence of a lactone is a common feature but its role in the anti-tumour activity of lignans is not clear e.g. burseran possesses a furan ring rather than a lactone ring and displays a degree of activity. Also it does not seem to picropodophyllin and picropodophyllic acid are both weakly active.



A major proportion of active lignans do not possess the 3, 4, 5 trimethoxyphenyl moiety which shows that it is not an essential requirement for activity. The methylenedioxyphenyl residue plays an important role in activity as many anti-tumour lignans possess this attachment. The basic skeleton of the active lignan is difficult to relate to its antitumour potential. It has been suggested that the skeleton layout may be an important factor with particular regard to podophyllotoxin but there is no particular trend shown in comparison with similar lignan structures.

To illustrate the above analysis, a study of the structure-activity relationships of podophyllotoxin and its analogues has shown the following trends:

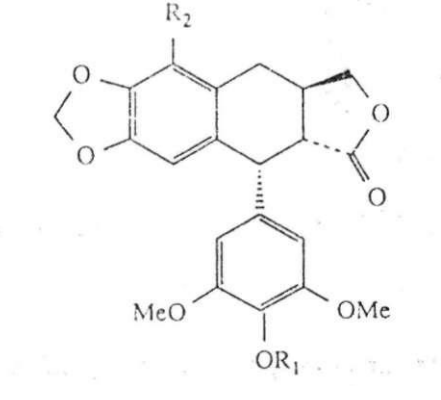
1. The configuration at C-4 seems to be important e.g., epipodophyllotoxin, is 10 times less active than its primer.



epipodophyllotoxin

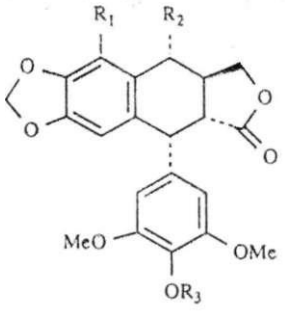
2. An OH group at C-5 rather than C-4 seems to increase activity *e.g.*, β-peltatin is more potent than podophyllotoxin.

3. The hydroxyl group at C-4 does not seem to be essential since desoxypodophyllotoxin and α-and β-peltatin are all active.



R_1= Me R_2 = H desoxypodophyllotoxin

4. Replacing the 4-OH with OMe decreases potency, also replacing OH with glucose in podophyllotoxin results in reduction of activity.

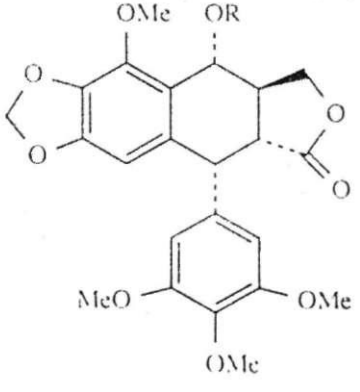


R_1	R_2	R_3	
H	OGlc	Me	podohyllotoxin glucoside

5. The configuaration at C-2 plays a significant role in anti-tumour activity *e.g.,* picropodophyllin has greatly decreased cytotoxic activity.

6. Substituting a furan ring for the lactone of podophyllotoxin greatly reduces antitumour activity.

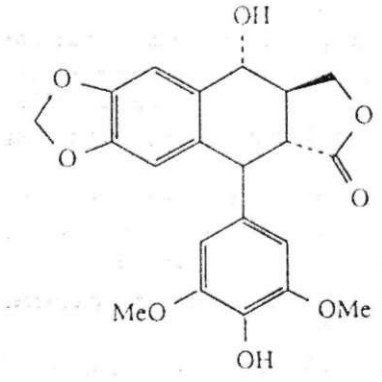
7. The polarity of substituents at C-4 are more important than their steric effect for anti-tumour activity *e.g.,* 5-methoxypodophyllotoxin glucoside is less active than its aglycone.



R = H 5 - methoxypodophyllotoxin

R = Glc 5 - methoxypodophyllotoxin glucoside

8. The three methoxy groups on the pendant ring do not seem to be essential for antitumour activity *e.g.,* 4'-demethylpodophyllotoxin has almost the same activity as podophyllotoxin.



4' - demethylpodophyllotoxin

Conclusion

Plant products have been used to treat cancer for many years. Forinstance, podophyllotoxins and other types of lignans have shown evidence of acticancer activity. Further studies will lead researchers to continue to uncover new active structures and several new compounds from plants which may be used in clinical trials. Perhaps future the plants will play an even more significant role than they do now.

REFERENCES

1. Lewis, **M.W.,** Medical Botany Awiley-Interscience Publication London, Sydney Toronto (1977).
2. **Andersan,** J.**F.,** An Illustrated History of the Herbals, New York Columbia University Press (1977).
3. Wagner, H., **and Wolff, J.,** New Natural Products With Pharmacological, Biological or Theraputical Activity (1976).
4. World Cancer, World Cancer Res. Fund News Letter Healthy Eating 3. (1990).

5] **Nishino,** H., **Iwashima,** A., Antitumor promoting activity of garlic extracts. *Ontology* **46,** 277 (1989).

6. Weiss, R.F., Herbal Medicine A.B. Arcanum Gotherburg Sweeden (1988).

7. **Dymock, W.,** Pharmacographia Indica, Re-printed by Hamdard The Journal of the Institute of Health and Tıbbi (Medical) Research, Pakistan, Zain Packaging Industries Ltd. Karachi 16 (1972).
8. **Massanet, G.M., Pando, E., and Rodriguez, F**.E., **Lignans,** *Fitoterapia IX* 3-35 (1989).
9. **Carter, S.K., and Livington R.B.,** Cancer Tretment Reperts Proceding of the 16th Annual Meeting of the Society for Economic Botany "Plant and Cancer" (1976).
10. **Cole, J.R., and Biachi, E., and Trumbull, E.R.,** Antitumor Agents from *Bursera microphylla, J. Pharm. Soc.* **58,** 175, (1969).
11. **Jolad, S.D.,** Antitumor activity of *Penstemon deustus. J. Org. Chem.,* 45, 1327 (1980).
12. **Ulubelen,** A., **Saiki, Y.Ü. Lotter, M., and Chari, V.M.,** Chemical components of *Strax officinalis IV, Planla Med.,* **34,** 403, (1978).
13. **Trums, S., and Eich, E.,** Cytostatic activities of Lignanolides from *Ipomoea cairica, Planta Med.,* **55,** 658, (1989).
14. **Skeria, M.G., and Amer, K.M.,** Lignans from *Haplophyllum tuberculatum, Phytochemistry* **23,** 1151, (1984).
15. **Murakami, T., and Maksushima,** A., The cytological effects of chemicals on Tumors, Yakugaku Zasshii **81,** 1596, (1961).
16. **Fukamiya, N., and Lee, K.H.,** Antitumor agents from *Justicia procumbens, J. Nat. Prod.* **49,** 348, (1986).
17. **Anjaneyulu,** A.**S.R., Ramajah, P**.A., **and Row, R.L.,** Lignans from *Cleistanthus collinus, Phytochemistry,* **14,** 1875, (1985.
18. **Anjaneyulu, A.S.R., Ramaiahi, P**.A., **Row, R.L., Venkatesworlu, R., Pelter,** A., Cyctotastic lignan isolated from *Cleistanthus collinus, Tetrahedron,* **37,** 3641, (1981).
19. **Ayres, D.C., and Loike, J.D.,** Lignans Cambridge University Press, Cambridge, New York, 28, (1990).
20. **Nakul, G.S., Zarga, M.H**.A., **Sabri, S.S., Al-Eisawi, D.M.,** Chemical constituents of the Flora of Jordan, *J. Nat. Prod.* **50,** 48, (1987).
21. **Gonzales,** A.**G., Darias, V., and Alanso, G.,** Cytostatic lignans isolated from *Hapolophyllum hispanicum, Planta Med.,* **36,** 200, (1979).
22. **Arar, G., and Gözler, T.,** *Haplophylum cappadocicum* spach üzerinde Fitokimyasal araştırmalar, *Doğa,* **11, (2),** 180, (1987).
23. **Weiss, S.G., Tin-Wa, M., Perdue, R.E., and Farnsworth, N.R.,** Potential Anticancer agents II. Antitumor and Cytotoxic Lignans from *Linum album, Pharm. Sci.* **64,** 95, (1975).
24. **Kupchan, S.M., Britton, R.W.,** Steganacin and Steganangin from *Steganotaenica araliaceae, J Am. Chem., Soc.* **95,** 1335, (1964).
25. **Tandon, S.F., and Rastogi, R.P.,** Wikstromol, a new lignan from *Wikstroemia viridiflora, Phytochemistry,* **15,** 1789, (1976).
26. **Mc Doniel, P.B., and Cole, J.R.,** Antitumor activity of *Bursera schlechtendalii* (Burseraceae), J. *Pharm. Sci.,* **61,** 1992, (1972).
27. **San Feliciano,** A., **Gordalizo, M.,** Antineoplastic and antiviral activities of some cyclolignans. *Planta Med.,* **59,** 246, (1993).

28. Pettit, G.R., and Schanfelberger, D.E., Isolation and structure of the cytostatic lignan Phyllanthostatin A, J. *of Nat. Prod.* 51, 1104 (1988).

29. Macrae, W.D., and Towers, G.H.N., Biological activities of lignans, *Phytochemistry*, 23, 6, 1207, (1984).

30. Jolad, S.D., and Wiedhopf, R.M., Cytotoxic Agents from *Bursera morelensis, XJ. Pharm. Sci.* 16, 6, 893 (1977).

31. Jolad, S.D., and Wiedhopf, R.M., Isolation of a new lignan Burseran, J. *Pharm. Sci*, 54, 659, (1977).

32. Kupchan, S.M., Hemingway, J.C., Tumor inhibitors XIX. Desoxypodophyllotoxin, the principle of *Libocedrus decurrens, J. Pharm. Sci.*, 64, 95, (9165).

33. Aynechi, Y., Desoxypodophyllotoxin, the ocytotxic principle of *Callitris columellaris, J. Pharm. Sci.*, 60, 121, (1971).

34. Kupchan, M., and Hemingway, J.C., Tumor Inhibitors VIII. J. *Pharm. Sci.*, 54, 659, (9171).

35. Fang-X., Dhamika, N., Poebe, C.H., Plant Anticancer Agents XXXVII, *Planta Med.*, 42, 346, (1985).

A.Ü. ECZACILIK FAKÜLTESİ DERGİSİNDE YAYINLANMASI İSTENEN MAKALELER İÇİN YAZARLARIN UYACAĞI KURALLAR

1— Fakültemiz Dergisi Mayıs ve Kasım aylarında olmak üzere yılda 2 sayı olarak yayınlanmaktadır. Yayınlanması istenen makaleler en geç 15 Nisan ve 15 Kasım tarihlerine kadar 3 nüsha olarak Dekanlığa gönderilmelidir.

2— Yayın Komisyonuna gelen makaleler, en az 2 danışmana gönderilir.

I- Dergide Yayınlanacak Yazı Türleri:

Dergide Eczacılık alanında ve daha önce hiçbir yerde yayınlanmamış aşağıda belirtilen türde makaleler yayınlanır.

1— Araştırma Makalesi: 10 daktilo sayfasını geçmeyen (Şekiller hariç) orijinal araştırmalar, araştırma makalesi olarak değerlendirilir.

2— Derleme: 15 daktilo sayfasını geçmeyen belirli bir konuda o güne kadar ki gelişmeleri yeterli literatür desteği ile ortaya koyan ve sonuçlarını yorumlayan yazılar derleme olarak değerlendirilir.

II- Yazım Esasları:

1— Dergiye Türkçe dışında İngilizce, Almanca ve Fransızca olarak yazılmış makaleler kabul edilir. Makaleler Türk Dil kurallarına uygun olarak yazılmalıdır.

2— Yazılar A-4 formatta kağıdın bir yüzüne normal puntolu daktilo ile 2 aralıklı olarak yazılmalı, kağıdın alt ve üst kenarından 2 cm., sol kenarından 3 cm. ve sağ kenarından 1.5 cm boşluk bırakılmalıdır.

3— Eserin yazım esasları aşağıdaki sıraya uygun olmalıdır:

Başlık, Türkçe ve Yabancı Dilde Özet, Anahtar Kelimeler, Giriş, Materyal ve Yöntem, Sonuç ve Tartışma, Kaynaklar. Derleme Makalelerde "Materyal ve Yöntem" Bölümü bulunmayabilir.

4— Türkçe ve Yabancı Dilde başlığın her kelimesinin baş harfi büyük harflerle yazılmalı, ilk başlık siyah, ikinci başlık beyaz olmalıdır.

5— Yazar veya yazarların adları küçük, siyah, soyadları büyük siyah harflerle başlığın altına; metin içinde geçen yazar adları büyük harflerle yazılmalıdır.

6— Siyah dizilmesi istenen kelimelerin altları yeşil, italik dizilmesi istenen kelimelerin altları siyah kalemle çizilmelidir.

7— Özetler makalenin baş kısmında verilmelidir. Türkçe ve Yabancı Dilde olmak üzere en çok 100'er kelimeden oluşmalıdır.

8— Anahtar kelimeler araştırmayı, tanıtıcı özellikte, Türkçe ve Yabancı Dilde olmak üzere en çok 5 kelimeden oluşacaktır.

9— Giriş Bölümü, yapılan araştırma ile ilgili önemli çalışmaların ve araştırmanın amacının belirtildiği bölümdür.

10— Materyal ve Yöntem: Bu bölümde kullanılan materyal belirtilir ve metod hakkında literatüre dayandırılarak kısaca bilgi verilir.

11— Sonuç ve Tartışma: Bulguların değerlendirildiği ve literatürdeki ilgili araştırmalarla karşılaştırmalar yapılarak sonuca varılan bölümdür.

12— Teşekkür var ise kaynaklardan önce yer almalıdır.

13— Kaynaklar, makalede parantez içindeki numaralarla belirtilmeli ve makale sonunda bu numaralara göre sıralanmalıdır. Kaynaklar aşağıdaki örneklere uygun olarak yazılmalıdır.

a) Makale:

Yazarın soyadı (siyah), adının başharfleri (siyah), makale adı, derginin adı (italik), cilt no (siyah), sayı (parantez içinde), sayfa numarası (başlangıç ve bitiş), yıl (parantez içinde) yazılmalıdır.

ÖRNEK: Matyus, P., Synthesis and Structure-Activity Relationship of Pyridazine Derivatives with Cardiovascular Activity, *Sci. Pharm.,* 58, 186—188 (1990)

b) Kitap

Yazarın Soyadı (siyah), adının başharfi (siyah), kitabın adı, cilt no (varsa) kitabevi, yayınlandığı şehir, sayfa numarası, basıldığı yıl (parantez içinde) yazılmalıdır.

ÖRNEK: Franke, R., Theoretical Drug Design Methods, Elsevier, Amsterdam, 130 (1984).

c) Editörlü Kitap

Yazarın soyadı (siyah), adının başharfi (siyah), bölümün adı, bölümün alındığı kitabın adı (parantez içinde), cilt no (varsa) editörün soyadı, adının başharfi, kitabevi, yayınlandığı şehir, sayfa numarası, basıldığı yıl (parantez içinde) yazılmalıdır.

ÖRNEK: Weinberg, E.D., Antifungal Agents (Burger's Medicinal chemistry), II, Wolff, M.E., John Wiley and Sons, New York, 531, (1979).

III- Diğer Konular:

1— Şekil altları, Şekil 1. . . . .olarak; Tablo üstleri Tablo 1. . . . . şeklinde yazılmalıdır.

2— Klişesi yapılacak grafik, şema, formül gibi şekiller aydınger kağıdına çini mürekkebi ile çizilmeli, şekillerdeki yazı ve rakamlar daktilo ile yazılarak küçültme oranları yazar tarafından belirtilmelidir. Her şeklin arkasına yazar adı ve kaçıncı şekil olduğu kurşun kalemle yazılmalıdır. İkinci ve üçüncü nüshalar için şekillerin fotokopileri eklenmelidir.

3— Fotoğraflar parlak kartona ve net olarak basılmış olmalıdır. Dergiye renkli fotoğraf koymak mümkün değildir.

4— Bölüm başlıkları beyaz büyük harflerle, alt başlıklar siyah küçük harflerle yazılmalıdır.